

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS, )  
INC., )  
Plaintiff, ) C.A. No. 18-651-CFC  
v. )  
TEVA PHARMACEUTICALS )  
USA, INC., et al., )  
Defendants. )

Monday, March 28, 2022  
8:45 a.m.  
Bench Trial

Volume 1

844 King Street  
Wilmington, Delaware

BEFORE: THE HONORABLE COLM F. CONNOLLY  
United States District Court Judge

APPEARANCES:

MORRIS NICHOLS ARSHT & TUNNELL  
BY: KAREN JACOBS, ESQ.  
BY: DEREK J. FAHNESTOCK, ESQ.

-and-

1 APPEARANCES CONTINUED:

2 PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP  
3 BY: NICHOLAS GROOMBRIDGE, ESQ.  
4 BY: ERIC ALAN STONE, ESQ.  
5 BY: JOSEPHINE YOUNG, ESQ.  
6 BY: DANIEL KLEIN, ESQ.  
7 BY: JENNIFER DENEALT, ESQ.  
8 BY: MICHAEL F. MILEA, ESQ.  
9 BY: JACOB M. BERMAN, ESQ.

10 Counsel for the Plaintiff

11 COZEN O' CONNOR  
12 BY: KERRY B. MCTIGUE, ESQ.  
13 BY: BARRY P. GOLOB, ESQ.  
14 BY: W. BLAKE COBLENTZ, ESQ.  
15 BY: KERI L. SCHAUBERT, ESQ.  
16 BY: DEREK R. GRETKOWSKI, ESQ.  
17 BY: AARON LUKAS, ESQ.  
18 BY: KAN EKINER, ESQ.

19 Counsel for the Defendant Apotex

20 SHAW KELLER  
21 BY: NATE HOESCHEN, ESQ.

22 -and-

23 STERNE KESSLER  
24 BY: J.C. ROZENDAAL, ESQ.  
25 BY: DEIRDRE M. WELLS, ESQ.  
BY: BYRON PICKARD, ESQ.  
BY: WILL H. MILLIKEN, ESQ.  
BY: SASHA S. RAO, ESQ.  
BY: MICHAEL BRUNS, ESQ.  
BY: WILL RODENBERG, ESQ.

Counsel for the Defendant Teva  
Pharmaceuticals U.S.A

P R O C E E D I N G S

(Proceedings commenced in the courtroom beginning at 8:45 a.m.)

**THE COURT:** Ms. Jacobs.

**MS. JACOBS:** Good morning, Your Honor. For Plaintiffs Vanda, Karen Jacobs and Derek Fahnestock from Morris Nichols. We have here at counsel table, Nicholas Groombridge and Eric Stone from Paul Weiss. And we have our client representative, Dr. Polymeropoulos.

Thank you, Your Honor.

**THE COURT:** Mr. Hoeschen.

**MR. HOESCHEN:** Good morning, Your Honor. Nathan Hoeschen from Shaw Keller on behalf of Defendant Teva. With me at counsel table, I have J.C. Rozendaal and William Milliken from Sterne Kessler. Behind, I have Deirdre Wells, also from Sterne Kessler. In the gallery, I have Byron Pickard, Michael Bruns, William Rodenberg, Sasha Rao; and from the client, Joseph Crystal.

**THE COURT:** Great.

Good morning.

**MS. EKINER:** Good morning, Your Honor. Kaan Ekiner from Cozen O'Connor. We represent the Apotex defendants. And this morning, with me at counsel table, I have Blake Coblentz from my firm's DC office.

1                   **THE COURT:** Great.

2                   **MS. EKINER:** Thank you, Your Honor. All right.  
3 Let's begin.

4                   **MR. STONE:** Good morning, Your Honor. Eric  
5 Stone for Vanda. I have three items by way of update, and  
6 one item that we have to bring before the Court for a  
7 resolution, which I hope will be quick.

8                   By way of update, all in the direction of case  
9 narrowing, then there were five. We are no longer  
10 asserting the '234 patent, which is one of the two patents  
11 involving the enzyme CYP1A2. And I should say, we've  
12 agreed with the defendants on this; they are not first  
13 learning this.

14                   We have also taken to heart the Court's  
15 comments about commercial success, and we will not be  
16 relying on commercial success as a secondary indicator of  
17 nonobviousness, which allows us not to call Dr. Grabowski  
18 and the defendants not to call Dr. McDuff.

19                   So that will shorten the case, although  
20 probably not by that much, but nevertheless, it will  
21 shorten the case.

22                   **THE COURT:** Okay.

23                   **MR. STONE:** In addition, the defendants have  
24 asked for permission to exceed the scope of our direct  
25 examination on our two fact witnesses during our

1 case-in-chief. On the one hand, that let's them talk  
2 about invalidity and other issues; on the other hand, we  
3 would like to streamline things so we have said yes to  
4 that. So they will be permitted to, and I presume they  
5 will, exceed the scope of the direct examinations for  
6 Dr. Polymeropoulos and Mr. Pandrapragada, which brings us  
7 to the one open issue.

8 We would like to call, as our first witness in  
9 our case-in-chief, Dr. Charles Czeisler to do a technology  
10 tutorial of about 25 minutes that is essentially just  
11 vocabulary that will come up. We have exchanged it with  
12 them. They have no objection to the content; they have no  
13 objection to the fact of there being a technology  
14 tutorial.

15 Their only objection is that Dr. Czeisler on  
16 the merits is a rebuttal witness. That's true. He is not  
17 going to talk about the merits. He is not citing a  
18 document, he's not talking about the patents, he's not  
19 even mentioning the drug. They agree that were it an  
20 infringement expert, they would have no objection. But  
21 they don't want us calling in our case-in-chief to give a  
22 technology tutorial a witness who on the merits is a  
23 rebuttal witness.

24 His expert report does say he will give a  
25 technology tutorial. This is not a surprise to them.

1 They are opposing it, that's where we are.

2 **THE COURT:** Not sure what on the merits. You  
3 want to put someone up to introduce technology?

4 **MR. STONE:** Yes, Your Honor.

5 **THE COURT:** And they've got an objection.

6 **MR. STONE:** That's right.

7 **THE COURT:** Okay. Well, let's hear them then.

8 **MR. ROZENDAAL:** Good morning, Your Honor. J.C.  
9 Rozendaal for Teva.

10 Now, the issue is the person -- the witness at  
11 issue, Dr. Czeisler, has put in only one set of expert  
12 reports on this case, and they are rebuttal reports to  
13 the -- on the issue of invalidity. And so he has said  
14 he's putting no opening expert report on anything having  
15 to do with their case-in-chief.

16 And it is true that in his rebuttal report on  
17 invalidity, he has a section of the report called  
18 Technology Introduction. But that technology  
19 introduction, as one might expect, is a self-serving  
20 analysis of the technology and the prior art designed to  
21 provide a lens through which the prior art is viewed.

22 We don't think it is appropriate for that kind  
23 of witness to give a technology tutorial or to say  
24 anything in their case-in-chief because we have the burden  
25 on infringement. We ought to be going first and last on

1 the question -- pardon me, on invalidity. We ought to be  
2 going first and last on the question of invalidity. And  
3 the pretrial order, Paragraph 118, makes very clear the  
4 order in which evidence is to be presented.

5 So what they are really saying is they would  
6 like to call their invalidity witness twice: Once in  
7 their case-in-chief to sort of talk -- and it's not true  
8 that we don't object to their giving a technology  
9 tutorial, and it's not true that they've told us what he's  
10 going to say. They have shared with us his  
11 demonstratives, and we objected to several of them.

12 So we don't know what's coming, and we don't  
13 think it's appropriate for them to sandbag us by putting  
14 all this in a rebuttal report on invalidity and then  
15 showing up the weekend before trial and saying, oh, by the  
16 way, we are going to call him twice, and we want him to  
17 talk right off the bat in our case-in-chief when he hasn't  
18 provided any expert report dealing with the issues in the  
19 case-in-chief.

20 It is also the case, of course, that they have  
21 an infringement expert who is going to be talking about  
22 the infringement; they have two witnesses who are named  
23 inventors on the patent-in-suit who presumably can tell us  
24 what the technology is. And so we don't understand the  
25 purpose of this additional tutorial, and we don't think

1 it's appropriate, given the way the evidence has come into  
2 the case.

3 **THE COURT:** Okay.

4 **MR. STONE:** Just a couple of brief points in  
5 response, Your Honor.

6 We met and conferred last night and spoke with  
7 their team, and we took out the two slides they objected  
8 to, and they confirmed they have no objection to this  
9 content with respect to the other slides.

10 To be clear, every lawyer, when they get the  
11 slides the night before, wonders what else will there be  
12 in the testimony that's not in the slides. I represented  
13 to them yesterday nothing; the slides are literally the  
14 contents of what he is going to talk about. So they do  
15 know what he's going to say.

16 In terms of the prior art and the gloss on the  
17 prior art, he will not be mentioning the prior art at all  
18 in the technology.

19 **THE COURT:** Why didn't you raise this in the  
20 pretrial conference?

21 **MR. STONE:** Your Honor, I apologize for -- we  
22 didn't raise it in the pretrial conference; we raised it  
23 with them a week ago. I didn't know it was going to be  
24 objected to. I didn't think it -- perhaps that's on me.  
25 I didn't think it was going to be controversial; that an



1 expert who was going to give a technology tutorial would  
2 give it at the beginning of the case. We didn't know it  
3 was an issue.

4 The notion we raised it this weekend is untrue;  
5 we raised it a week ago. But that having been said,  
6 that's where we are. And if the Court wants it to wait  
7 until -- Dr. Czeisler is our last witness so --

8 **THE COURT:** Let's wait. Go ahead.

9 **MR. STONE:** I'm sorry?

10 **THE COURT:** Let's just wait. It is a rebuttal  
11 witness; save it for rebuttal.

12 **MR. STONE:** Okay.

13 **MS. JACOBS:** Your Honor, just a very last  
14 issue.

15 Dr. Polymeropoulos is an inventor on some of  
16 the patents-in-suit. He will be a fact witness. He is  
17 our corporate representative. I just wanted to check and  
18 see if the Court is comfortable with him being here at  
19 counsel table during openings. Just for sensitivity from  
20 a prior case, we want to make sure that's --

21 **THE COURT:** The prior case was an inventorship  
22 issue, though.

23 **MS. JACOBS:** It was, Your Honor.

24 **THE COURT:** What's he going to be testifying  
25 about here?

1                   **MR. GROOMBRIDGE:** Your Honor, he will be  
2                   testifying about the history of the invention. And to  
3                   some extent, I'd like to touch on the patents themselves.

4                   **THE COURT:** What's the position of the  
5                   defendant?

6                   **MR. ROZENDAAL:** No objection to him staying,  
7                   Your Honor.

8                   **THE COURT:** All right. He can stay. Thank  
9                   you.

10                  **MS. JACOBS:** Thank you, Your Honor.

11                  **MR. GROOMBRIDGE:** Then we are ready to proceed  
12                  with our opening statements. We do have hard copies of  
13                  the slides, if that is useful.

14                  If I may approach.

15                  **THE COURT:** Sure. Please.

16                               **PLAINTIFF'S OPENING STATEMENT**

17                  **MR. GROOMBRIDGE:** Good morning. So, Your  
18                  Honor, I will begin with, I guess, a table of contents.  
19                  So what we've done here, I will be talking about the  
20                  background of the case and some of the history.

21                  We have divided the patents. As Mr. Stone  
22                  said, we dropped one, so there are now five remaining  
23                  patents. We've divided them into three categories here.

24                  And just to jump right into the background,  
25                  Vanda is the patent holder and the plaintiff in this case.

1 Vanda is a relatively small company by the standards of  
2 the pharmaceutical industry. It was founded in 2003. As  
3 Ms. Jacobs mentioned, we have with us as our client  
4 representative Dr. Polymeropoulos, who is the founder and  
5 chief executive of the company.

6 And Vanda's business model is that it takes  
7 drug candidates that have been discontinued by other  
8 companies, usually much larger companies, and tries to  
9 overcome whatever was the obstacle with that candidate  
10 molecule and bring it to market to meet what would  
11 otherwise be unmet medical need. And so what Vanda does  
12 is take things that other people gave up on. And it has  
13 at the moment two marketed products, both of which fit  
14 this exact profile.

15 The one in this case is Hetlioz; the other one,  
16 the subject of earlier litigation. I mention it only  
17 because I suspect when we get around to the briefing, Your  
18 Honor may be seeing a Vanda case that involved the other  
19 product that was litigated in this Court several years  
20 ago.

21 As I mentioned, there are the patents. We have  
22 one asserted claim from each patent, and I will walk  
23 through them as we get to them. The way we've broken them  
24 up, there is a -- probably the central patent, or the ones  
25 that make sense to begin with, is this reissue '604, which

1 involves the method of treating a condition called Non-24  
2 Sleep-Wake Disorder, which I think we will probably all in  
3 the course of the trial get around to calling Non-24.

4 There are, then, three other method of  
5 treatment patents that involve drug interactions and the  
6 effect of food in terms of using this molecule,  
7 tasimelteon, to treat Non-24. And then there is another  
8 patent that is involved in how one controls for impurities  
9 in the product.

10 And the first of the -- four of the five  
11 patents -- the first four are listed there -- are all the  
12 claims that are asserted are all specific to the condition  
13 Non-24. So what I wanted to do is talk about what that  
14 condition is, and it is a circadian rhythm disorder that  
15 occurs primarily in blind people. It's chronic; it's  
16 lifelong; there's no cure for it.

17 And what happens in this condition is that the  
18 sufferer's sleep-wake cycle drifts. It moves later and  
19 later every day and essentially rotates around the  
20 calendar. And because of the way the body's circadian  
21 rhythms work -- a subject that we will get into -- it  
22 makes it very difficult to sleep at night and very  
23 difficult to stay awake during the daytime.

24 And the effects of this on the sufferers are  
25 quite severe: Fatigue, cognitive impairment, often also

1 metabolic problems. It's frequently accompanied by  
2 depression, anxiety, and other psychiatric conditions. I  
3 think we will hear evidence of people saying that they  
4 find the Non-24 worse than the blindness itself. And it  
5 effectively, for many sufferers, means they can't engage  
6 in a normal life in society.

7 And that is the condition.

8 Importantly, Your Honor, Non-24 is a problem  
9 with sleep timing; it's not fundamentally a problem with  
10 sleep duration. And when I first came to this case, I  
11 thought this sounded like it was a sleep medicine, a  
12 soporific. That's not true.

13 The perturbed sleep patterns may lead to  
14 insufficient sleep. But that's not the underlying  
15 problem. The underlying problem is that the person's body  
16 wants to sleep at the wrong time of day. And the reason  
17 for that involves the body's circadian rhythm. The  
18 circadian rhythm, we will get into this in a little more  
19 detail, but it involves something that is often called the  
20 master body clock located in the brain which controls a  
21 host of daily rhythms. They affect many, many aspects of  
22 the body's function, not just sleep but immune response,  
23 metabolism, many, many other things.

24 And left to themselves, the circadian rhythm of  
25 all human beings follows a cycle unique to that

1 individual, that is roughly, but not exactly, 24 hours.

2 And so that -- in the science, that cycle of each  
3 individual is called tau or referenced by the Greek letter  
4 that we see there.

5 And what it means is it is -- for most people,  
6 it is somewhat more than 24 hours; for some people it  
7 might be less than 24 hours. But in this case, I think we  
8 will be focusing on the more.

9 And here, we see that's a 24-hour cycle.  
10 Someone's tau might be 24.5. Might be that the body's  
11 rhythm is set to a cycle of 24 and a half hours, and this  
12 would be a tau of 24.5.

13 Now, another thing that will be important in  
14 the case is daily sleep period. And we will present  
15 evidence of this, and what that evidence will say is that  
16 the way that the natural day is divided up and the way the  
17 body reacts to it is that there is a nighttime period in  
18 which there is a biological propensity for us to sleep.

19 And there is a daytime period, or natural day,  
20 and now, in the modern world evening, where we have light.  
21 And this gives us a biological propensity for wakefulness.  
22 And the daily sleep period is a period of time -- it  
23 doesn't -- it's not a period during which the individual  
24 must be asleep throughout that period, it's a sleep  
25 opportunity or a window of time into which sleep will

1 naturally be consolidated. And so for the vast majority  
2 of people, they -- what they will want to do is get their  
3 sleeping done preferably in one go during the nighttime.  
4 That's a daily sleep period.

5 The circadian rhythms, what happens here, just  
6 to go into a little bit more detail on this aspect of  
7 drift, of the problem here, is that if we take someone who  
8 has, by way of example, that internal cycle of 24.5 hours,  
9 what that will mean is absent some form of intervention,  
10 some cue to reset the body clock, every day that person's  
11 natural cycle will drift half an hour later. So someone  
12 who is fully aligned yesterday will be half an hour out of  
13 alignment with the external day/night cycle today. And  
14 every single day that will happen.

15 So in this instance, by the end of next week,  
16 that person would be fully six hours out of alignment.  
17 Instead of their body saying, I would like to go to sleep  
18 at 11:00 p.m., it would now be saying, I'd like to go to  
19 sleep at 5:00 a.m.

20 And this will continue. In this example, the  
21 individual would cycle around the entire 24 hours in eight  
22 weeks, and so they would come back. They would briefly be  
23 realigned with all the rest of us, and then the cycle  
24 would repeat itself.

25 This is the condition Non-24.

1           And what causes it -- the reason why this  
2           doesn't happen in healthy people, is that the body resets  
3           itself, its internal clock, every day using light. And so  
4           what we have in this demonstrative, we have our daily  
5           light/dark cycle there on the left. The eye, the retina,  
6           which has in it specialized cells, not just the rods and  
7           cones that give us vision, but in addition to that there  
8           are other cells whose job is to detect light and tell the  
9           brain about the light.

10           And they convey that signal to something called  
11           the suprachiasmatic nucleus, which is a group of neurons,  
12           in fact two groups of neurons within the brain, that is  
13           frequently called the master body clock. Or I think we  
14           will hear it analogized to the conductor of an orchestra.  
15           But what it does within the body is to keep all the other  
16           body rhythms, for which the daily cycle matters, on the  
17           same cycle.

18           And another thing that will be important here  
19           is the pineal gland. The pineal gland releases melatonin,  
20           the chemical melatonin, the natural substance, into the  
21           blood stream. And melatonin is a hormone. We will be  
22           talking a lot about melatonin. It is sometimes called the  
23           hormone of darkness. And what it does is it tells our  
24           bodies to sleep.

25           And we see there that trace that's at the top.



1 That is a trace showing the level of melatonin released  
2 from the pineal gland into the body as we compare it  
3 against evening, nighttime, and daytime. And we can see  
4 that the -- it starts to climb. It's about -- it  
5 typically begins, that onset of melatonin release, begins,  
6 typically, one to two hours before sleep. And that's what  
7 tells us to go to sleep. And then as it ebbs away, that's  
8 what tells our bodies to wake up. This is the sleep  
9 cycle.

10 And just to be clear, Your Honor, it will be  
11 important, in the case that we're differentiating between  
12 this type of melatonin, that the body releases, which is  
13 what we would call endogenous, comes from within the body,  
14 versus exogenous melatonin. You can take melatonin as  
15 a -- I will call it a drug, but it's not actually  
16 regulated as a drug by FDA. You could go -- in fact, I  
17 did go to Walgreens and buy a bottle of it. You can buy  
18 this. And one of the things we will be hearing about is  
19 what happens is if you take melatonin in order to try to  
20 influence your sleep cycle.

21 So what would -- just to, again, run this  
22 through, what would happen is the eye detects light, that  
23 conveys a signal to the SCN, the SCN in turn conveys a  
24 signal to the pineal gland, the pineal gland releases  
25 melatonin. And every day because that clock is reset, due

1 to our perception of light, that holds the sleep rhythm in  
2 synchronization with the light/dark day outside.

3 Now, in a sufferer of Non-24, what happens is  
4 someone who has no circadian photoreception, who, for  
5 example, someone who is blind and their eyes no longer  
6 function, this can't happen. And now the process -- the  
7 timing of the process defaults to that tau, the internal  
8 body rhythm. And what that means then is, just another  
9 way of looking at the same information, that melatonin  
10 signal telling the individual to go to sleep drifts later  
11 and later every day.

12 So in our example here, by April the 8th, the  
13 person who was on a normal cycle yesterday, now their  
14 daily sleep period will be entirely in the daytime. And  
15 this is what's going on and what causes the disease or the  
16 condition.

17 Hetlioz is the only FDA-approved treatment for  
18 Non-24. And, indeed, it is the only drug that's been  
19 approved to treat the cause of a circadian rhythm disorder  
20 rather than the symptoms. And the way it works is it  
21 replaces light. Instead of lights providing that daily  
22 clock reset, the drug provides the daily clock reset. And  
23 that's called "entrainment" or synchronizing. And I don't  
24 doubt that in the trial we will be talking a great deal  
25 about that.

1           Now I would like to talk about the development  
2 of Hetlioz. And it begins with the large pharmaceutical  
3 company Bristol-Myers Squibb I'm sure Your Honor is  
4 familiar with. Bristol-Myers Squibb were the ones who  
5 created the molecule tasimelteon. And at some point in  
6 the 1990s, they got interested in this, and they began to  
7 develop it.

8           They applied for and obtained a patent, which  
9 I'm sure we will be hearing about. They did clinical  
10 trials. They began with a study in insomnia in elderly  
11 people. And then they started -- also they did a little  
12 preliminary work looking at what's called shift work sleep  
13 disorder. As you would imagine, Your Honor, people who go  
14 on shift work, they have circadian problems because they  
15 are suddenly telling their bodies they need to sleep  
16 during the daytime, for example.

17           I think what we'll hear is that when BMS got  
18 the results of their insomnia trial, the drug didn't work  
19 in that trial. It was no different from placebo. And in  
20 the way of large drug companies, they pulled the plug.  
21 They stopped the development of the product and just put  
22 it on the shelf and nothing happened for five years.

23           And then Vanda, which had just recently been  
24 created, came to them and said, we are interested in this.  
25 And they had a discussion, and Vanda did a deal with BMS

1       whereby it acquired the entire franchise. The terms of  
2       the deal were that Vanda paid an upfront payment of  
3       \$500,000, and they got everything that BMS had on  
4       tasimelteon. And there were further payments, milestone  
5       payments and royalties that would come into play if the  
6       product proceeded in development and got eventually to be  
7       sold. But the \$500,000 is, as I suspect Your Honor is  
8       aware, is a very, very low number, right, in the scheme of  
9       acquiring a franchise to a potential pharmaceutical. And  
10      it shows us that BMS had essentially given up on this and  
11      wanted no more of it.

12               So this is -- once Vanda took it over, this is  
13      what Vanda did. They began looking at it for what is  
14      called transient insomnia. And that is like jetlag would  
15      be a good example. It's not the only example, but -- and  
16      I will talk a little more in a moment about jetlag, but  
17      that is another circadian rhythm problem. And they did  
18      clinical trials on transient insomnia.

19               They also later did clinical trials on chronic  
20      insomnia. Those, at least so far, have not come to  
21      anything. The product has not been used, it has not been  
22      approved for use in those.

23               And after about five years, in sometime around  
24      2009, Vanda changed its focus and decided to direct its  
25      efforts to developing the product for Non-24. They had

1 known about Non-24, but they had elected for the first  
2 part of the development not to focus on that.

3 And so in 2010, they asked the FDA, and got  
4 granted, orphan drug status, which as Your Honor may know  
5 is what you get if the patient population is 200,000 or  
6 fewer, you get certain protections if you can get a drug  
7 approved, certain exclusivity. They got orphan drug  
8 status.

9 They began doing clinical studies, and there  
10 were two clinical studies really joined together here:  
11 SET and RESET. And the way a clinical trial is SET --  
12 there is an abbreviation which stands for Study of  
13 Efficacy of Tasimelteon. And SET, the SET trial, which  
14 was the largest clinical trial -- the SET and RESET trials  
15 together were the largest clinical trial ever conducted in  
16 the blind for a treatment like this. And they -- we will  
17 hear a lot of about them.

18 The SET trial proved that tasimelteon was  
19 capable of entrainment of blind people suffering from  
20 Non-24. And the RESET trial, which was an adjunct to it,  
21 proved that it was capable of maintaining the entrainment.

22 And after that, Vanda went to FDA, they filed  
23 an application for approval, they went back and forth with  
24 the FDA that I'm sure we will hear about, and they  
25 received FDA approval in 2014.

1           This is one of the -- this is from the first  
2 document, really, as they were setting out in 2004 to  
3 decide what to do. And they are talking about circadian  
4 rhythm sleep disorders, and they note there, there are  
5 seven recognized subtypes.

6           The reason I call that out, Your Honor, is I  
7 believe what we're going to hear from -- the defendants  
8 are going to try to blur together all circadian rhythm  
9 sleep disorders. They are going to say one is much the  
10 same as another. And when they look at things like the  
11 prior art, they are just going to say, ah, if it says  
12 circadian rhythm sleep disorder, that's fine.

13           We think the truth is, and the evidence will  
14 show, that these different circadian rhythm sleep  
15 disorders, are quite different one from another. In  
16 particular Non-24 is different and for reasons that I will  
17 come to.

18           But what we note here at the beginning, Vanda  
19 said, we initially plan to develop that code number --  
20 that was the internal BMS development number for  
21 tasimelteon, we plan to develop that for shift work and  
22 jetlag disorder. And we will potentially develop it for  
23 Non-24. So they said, we will go after shift work and  
24 jetlag, we might go after Non-24.

25           And the reason that was a "might" is what they

1 go on to say in the last call-out: Because trying to  
2 figure out whether tasimelteon would work for Non-24 will  
3 be complex and clinical trials will be difficult. It's a  
4 small patient population. It's very hard to find people  
5 to do this, and if you don't have enough people you don't  
6 have a -- you don't have a statistically significant  
7 answer, you just can't move the thing forward. You can't  
8 tell if it works.

9 And I think we'll hear -- in fact, I will touch  
10 on it myself in a moment -- how difficult it was to do the  
11 work that was necessary to prove whether tasimelteon could  
12 or could not entrain these people.

13 Another thing that they noted in the same  
14 document was that the manufacturing process they had  
15 acquired, inherited from BMS was problematic. It was  
16 difficult and expensive. And one of the things that we  
17 will hear evidence about is the product that BMS's process  
18 produced was not very clean. It included a lot of  
19 impurities. It was good enough just barely for clinical  
20 studies, but there was no way that it could have been used  
21 to make a product that would actually be approved and out  
22 in the world.

23 So now, I will start with the -- talking about  
24 what we are calling the reissue patent or the Non-24  
25 treatment patent. And, again, I would like to go into a

1 little bit more about the science. Talking about phase  
2 shifting. Phase shifting is a term we are going to hear,  
3 and I will use jetlag as an example.

4 So if we were to go from, let's say, New York  
5 to London, of course UK local time would be different. It  
6 would be five hours ahead of New York. And what that  
7 would mean, and this is what is jetlag, is that for the  
8 people in London adjusted to London time, they would have  
9 an endogenous melatonin signal that looks like the black  
10 line. This is the same type of information as I showed  
11 you before, Your Honor, but it's now presented in a linear  
12 fashion from one day to the next.

13 However, the person who's arrived from New  
14 York, that person's endogenous melatonin cycle would look  
15 like the red dashed line. It's out of phase. And this is  
16 why that person would have jetlag, would find it hard  
17 going to sleep at nighttime, and then would want to sleep  
18 until midday or later. That's jetlag. This is why we get  
19 jetlag.

20 Now a phase shift, which is a term I think we  
21 are going to hear a lot about, means a one-time pull. If  
22 I can do something that will pull that person's internal  
23 melatonin rhythm back to where it would be -- where they  
24 are adjusted to being in London, I will deal with the  
25 sleep problem. And that's what we call a phase shift. In



1 other words -- sorry. That kind of movement that -- in  
2 that direction would be a phase delay, I'm moving it later  
3 in time; in this direction would be a phase advance.  
4 Collectively that's called a phase shift.

5 Now, how does that relate to entrainment?  
6 Entrainment is more complicated. Entrainment involves the  
7 same type of thing, but it requires is a cue, a shifting  
8 of the clock every day. Not just once, as in jetlag  
9 paradigm, but phase shifting is, as I am looking at it,  
10 one single point in time, how can I pull this forward or  
11 pull it backward. Entrainment means I have to readjust it  
12 every single day. So I've got to have -- be able to pull  
13 the errant melatonin cycle to the place where I want it to  
14 be where it's synchronized, and then I have to be able to  
15 hold it there.

16 And that turns out to be more difficult to  
17 accomplish and involves a lot more issues.

18 Here, we see this is an unentrained person  
19 drifting later every day. And to entrain them, I've got  
20 to pull this back like that, and then be able to hold it  
21 there. And that means I have to be able to phase shift.  
22 A phase shift is a necessary, but not sufficient,  
23 condition. And that, I think, is going to be very  
24 important in the case.

25 You have to be able to phase shift. But the

1 mere fact that you can't phase shift doesn't tell you this  
2 will be possible. Why is that? Well, for example, I  
3 could have a situation where I have a drug that is capable  
4 of phase shifting, but not enough.

5 And so here in the pink, what I've done is --  
6 if someone takes this drug every day, it will change their  
7 cycle, but it will not entrain them; it will pull them  
8 back. In this instance, they are now -- their daily  
9 cycle, their tau is shorter, but they're still drifting  
10 and they still have the same problem.

11 And so in order to be able to entrain, we need  
12 to have a sufficient phase shift, that it can capture the  
13 cycle, pull it into alignment and then hold it in  
14 alignment. And all of that turned out to be quite  
15 challenging.

16 There's another concept here, Your Honor, that  
17 will be very important, I think, in the trial, which is  
18 what's called a phase-response curve.

19 Now, it turns out that if I take something like  
20 melatonin, exogenous melatonin, right, the effect of that  
21 on my sleep depends greatly on when in time I take it.  
22 Same pill, but I take it at different points in the day.  
23 And if I take it before 1:00 a.m., it causes an advance,  
24 it pulls my rhythm forward. If I take it after 1:00 a.m.,  
25 it causes a delay. And you can plot that out in a curve

1       like this. Right.

2               This is called a phase-response curve. And one  
3       of the things that this means, is if you're looking at  
4       something like melatonin itself or a drug like  
5       tasimelteon, it is critically important for purposes of  
6       entrainment when the patient takes that. Right.

7               And another factor that's in play here is not  
8       just how big of an effect will it have when I take it,  
9       right, but if the drug stays in the patient's body, it  
10      will cause an advance here. But if it's still around a  
11      few hours later when we get to this point, it will cause a  
12      delay. And so the same drug will counteract itself. And  
13      we might analogize that to a tug of war.

14              What is going on is that how long the drug  
15      remains in the body is vitally important. Because if it's  
16      too long, if the exposure of this is too great, then it  
17      will unbalance itself, and we will end up with, possibly,  
18      no net advance. And we see this. This is actually a  
19      publication by one of the defendants' experts talking  
20      about a concept called spillover.

21              Spillover is when you start in the right part  
22      of that phase-response curve, but the drug persists  
23      because you've given too big of a dose or because the body  
24      can't clear it. And so you get to the wrong part of the  
25      curve and now it starts counteracting itself.

1           So what this means is that dosage, time of  
2       administration, and exposure, how long the effect lasts in  
3       the body, are critically important to the ability to  
4       entrain.

5           And I think what we will hear, I think it will  
6       be conceded, is that while there was a phase-response  
7       curve known in the prior art for melatonin, there was no  
8       phase-response curve then, or even today, for tasimelteon.  
9       People simply don't know how tasimelteon behaves with  
10      respect to these characteristics.

11          So one other thing, Your Honor, that we believe  
12      will be important here is that the -- because of this  
13      problem with spillover, with timing and spillover, it's  
14      very important that you have a short sharp pulse in order  
15      to effectuate this treatment.

16          In other words, you want -- when the patient  
17      takes the drug, you want their body to see a lot of it  
18      quickly so it can grab hold of that cycle and, in effect,  
19      phase shift. But having done so, you want it to go away  
20      quickly so that it's not staying around and carrying over  
21      into the wrong part of the phase-response curve and  
22      undoing the work that it's just done.

23          And so one of the reasons I've come to this,  
24      reasons why things like drug interactions are a matter  
25      here is because in order for this to be effective, you

1 need to have that kind of profile; a rapid release and  
2 then a quick clearance. And we'll see some more curves  
3 like this.

4 So here's -- I'll go fairly quickly through  
5 this, at least I'll try. The SET trial was, as it says  
6 there, the largest trial ever conducted in this  
7 population. And you see there, Your Honor, they had to --  
8 they started -- they screened a lot of people. They  
9 assessed nearly 400 for eligibility in order to get 84  
10 into the treatment phase. And then they had a very, very  
11 complicated profile -- I won't go through these now -- a  
12 lot of very complicated results that were analyzed.

13 And when the results from this came out, this  
14 is what showed for the first time, the tasimelteon could,  
15 in fact, entrain sufferers from this condition.

16 Now, if you turn to infringement of this  
17 patent, I think we're going to have really two issues  
18 around infringement. The first one will be entrainment,  
19 and the second one will be a daily sleep period of  
20 approximately seven-to-nine hours.

21 Now, entrainment -- and Your Honor, as I'm sure  
22 Your Honor is aware, in the context of an ANDA case, a  
23 method of treatment patent, the key question is whether  
24 the proposed label that the generic would use, which is,  
25 of course, by law substantially identical to the

1 innovator's label, whether that label encourages,  
2 recommends or promotes infringement. And I think we're  
3 going to have a lot of evidence about that point.

4 On entraining, what the defendants are going to  
5 say is the word "entrainment" does not appear in the  
6 label, which is correct. And I think what they're going  
7 to say is that Vanda wanted it to be in the label and the  
8 FDA wouldn't put it in the label.

9 And the -- and it's certainly true, the word  
10 "entrainment" does not appear anywhere in the label. But  
11 in our view, Your Honor, there are other things in the  
12 label that make it perfectly clear to the sleep doctor to  
13 whom this label is directed, that what is going on here is  
14 entrainment. And I'll just call out some of those things.

15 The label says, tell your patients to take it  
16 at the same time every night. The reason is because for  
17 the -- as we just saw, timing of administration is  
18 critically important. It says, if you can't take it at  
19 the right time, skip it. And the reason for that, as a  
20 sleep doctor would know, is that the problem if you take  
21 it at the wrong time, you will interfere and compromise  
22 that process of entrainment that is going on.

23 And also it says that because of individual  
24 differences in circadian rhythms, you may need to take it  
25 for weeks or months. Because, as a sleep professional

1 would know, entrainment -- everyone has a different cycle,  
2 and depending on where they are in the cycle when you  
3 take -- you start taking the drug, and depending on how  
4 long that tau is, right, it will take more or less time to  
5 entrain. And so a sleep professional or medical  
6 professional reading these things would know exactly that  
7 what they're talking about is entrainment.

8 And perhaps the most important thing here on  
9 the label, with respect to the clinical studies -- this is  
10 talking about the RESET study -- it says this, it says:  
11 RESET is a study where patients had entrained. And the  
12 purpose of the study was to see whether tasimelteon could  
13 keep them entrained.

14 And so in this study, they did a -- they  
15 treated people with tasimelteon for 12 weeks to entrain  
16 them. And then it goes on to talk about what happened  
17 after that.

18 And it says here: Patients in whom the  
19 calculated time of peak melatonin level. Melatonin  
20 acrophase -- that's a term used for peak melatonin  
21 level -- occurred at approximately the same time of day in  
22 contrast to the expected daily delay. That is  
23 entrainment, Your Honor. That's saying that your  
24 melatonin cycle was pulled so that it was consistent, and  
25 the peak was coming at the same time every day, rather

1       than drifting later.

2               And we think the evidence will show that anyone  
3       who is any medical professional active in this field would  
4       understand that. Defendants' expert agreed at his  
5       deposition that that language would be understood to mean  
6       entrainment; you would know the person is entrained. And  
7       a clinician who treats Non-24 would certainly understand  
8       that.

9               And now, I have every expectation that  
10       Dr. Winkelman's testimony here in court will be consistent  
11       with what he said at his deposition.

12              And so even though the word "entrainment" may  
13       not be there, the concept of entrainment is absolutely  
14       there.

15              And I will move on, if that's okay, Your Honor.

16              Now, with respect to daily sleep period, I  
17       would not -- certainly not expect Your Honor to remember  
18       this, but we had some discussion of this at the claim  
19       construction hearing, and the construction that Your Honor  
20       decided on is plain and ordinary meaning.

21              I do think that we may have a dispute -- still,  
22       perhaps, on the claim construction issue, or something  
23       that at least tiptoes up to claim construction -- which is  
24       the patent says -- and this first call out, this is where  
25       the first introduction in the patent of this idea, daily



1 sleep period, and it says, for example, approximately  
2 seven-to-nine hours -- immediately goes on to say,  
3 understanding, of course, that the patient may not  
4 actually sleep during the entire period.

5 And so given that language, not surprisingly,  
6 both sides agree that it is not necessary that the patient  
7 sleep for all of the daily sleep period. However, there  
8 may be a disagreement, because I think that the  
9 defendants' view of the world is that you don't have to be  
10 asleep continuously for seven-to-nine hours. You could  
11 wake up because you have a bad dream, you could wake up to  
12 go to the bathroom. But essentially you have to be --  
13 their view is, you should be asleep for essentially all  
14 the rest of that period.

15 And our view is, that's just not correct.  
16 Right. That this is not saying -- it's not talking about  
17 sleep duration. It's talking about the window of time  
18 into which you want to consolidate your sleep.

19 And so we see another example here in the  
20 patent, someone who went to bed at 10:30, woke up at 6:30,  
21 so a sleep period of eight hours, but reported sleep time  
22 of five hours.

23 And in our view -- and I think we'll hear that  
24 the usage in the field is such -- that daily sleep period  
25 doesn't mean sleep duration. It means the window of time

1 to which you wish to consolidate your sleep.

2 And if that is the meaning, then in our view  
3 the label certainly talks about that. Again, it doesn't  
4 use the term "daily sleep period," but it talks about  
5 nighttime. And for the vast majority of the people,  
6 nighttime is the daily sleep period, the period into which  
7 they wish to -- they want to consolidate their sleep. And  
8 it differentiates total sleep time from nighttime. Right.

9 And so we think, Your Honor, the evidence will  
10 be that a medical professional reading this label would  
11 understand completely that it is, indeed, directing --  
12 that in the method that people will try to consolidate  
13 their sleep into a period of approximately seven-to-nine  
14 hours, not that they must sleep seven-to-nine hours.

15 So I'll talk briefly about validity and then  
16 move along in the interest of time.

17 One of the things -- there is an anticipation  
18 argument that is based on the website clinicaltrials.gov.  
19 And Your Honor may be aware that, in modern times, the law  
20 requires if you're going to do a clinical trial, you must  
21 provide information about that trial project to the  
22 government, who will then make it public on the website  
23 clinicaltrials.gov.

24 And one of the issues and -- so that the --  
25 this argument is based on a submission by Vanda to

1 clinicaltrials.gov describing what was to become the SET  
2 trial. And the argument is made that, well, because that  
3 was public, it rendered the results obvious.

4 Now, on the merits, Your Honor, we think that  
5 that's not true. Right. To ask the question is not to  
6 answer it. And for all the reasons that I have been  
7 alluding to it, it was neither known or knowable. It was  
8 not predictable prior to that clinical trial whether  
9 tasimelteon would or would not be able to entrain Non-24  
10 sufferers. And so we don't think that this does  
11 anticipate.

12 And we also think that there's a dispute around  
13 whether the defendants can prove that it was, in fact,  
14 publicly available early enough to count as prior art.  
15 And I suspect we will be digging into that as the evidence  
16 comes in. Right. It's, of course, their burden to prove  
17 that it was publicly accessible early enough. And I think  
18 that will be a point of dispute in the trial.

19 I have several prior art references that they  
20 rely on, in addition to the clinical trials data with  
21 reference to -- in support of an obviousness argument.  
22 These are predominantly Vanda's own work, Vanda's work  
23 from that period of four or five years, when they were  
24 focusing on other applications, potential other  
25 applications of tasimelteon like insomnia. So here's one

1 of the publications.

2 Lankford, the author, was a consultant to Vanda  
3 in this report of Vanda's work. It's about insomnia. It,  
4 again, mentions this clinical trial, that the fact that  
5 the clinical trial is ongoing. It doesn't talk about  
6 timing of administration.

7 So we think there are key things that are  
8 missing from this. Things that are vitally important for  
9 the Non-24 may not matter so much for insomnia.

10 The other reference I'll look at is something  
11 called the '244 publication. This is a Vanda patent  
12 application that is based on the earlier studies they did,  
13 focused on jetlag. Again, we think there are many things  
14 that are missing from this. That certainly would not tell  
15 a skilled person, or suggest to a skilled person that  
16 tasimelteon would be effective for treating Non-24.

17 I'll call out one that the dose here, the dose  
18 that suggests that this work says, the only dose that was  
19 shown to be effective for phase shifting was  
20 100 milligrams.

21 **THE COURT:** Is DLMO phase shifting?

22 **MR. GROOMBRIDGE:** Yes. DLMO is an acronym that  
23 stands for dim lights melatonin onset. And if Your Honor  
24 recalls, that curve where the pineal gland starts to  
25 release melatonin. And it climbs rapidly, and after an

1 hour or two, tells us to go asleep.

2 That point at which it begins to release  
3 melatonin, that's called DLMO, D-L-M-O. A lot of folks in  
4 the field call it DILMO.

5 And now, we talk about the drug-drug  
6 interaction patents and food effect patents. So these are  
7 things that built on the work that is described in the  
8 reissue patent, and that came from the SET and RESET  
9 clinical studies.

10 And one of the things that Vanda looked at here  
11 is metabolism, how the drug is metabolized. And this is  
12 what you might think of as a map of metabolism. The --  
13 this in the box in the middle, that's tasimelteon. And  
14 we'll hear quite a bit, I believe, about this.

15 This notation, CYP2 -- CYP1A2, for example,  
16 that refers to an enzyme that is produced in the body  
17 that's involved, or can be involved, in the metabolism of  
18 drugs. CYP is -- means something called Cytochrome P450.  
19 And there's a whole family of enzymes that are produced  
20 mostly in the liver, that are involved in breaking down  
21 drugs. In fact, 90 percent of drugs are metabolized by a  
22 handful of these enzymes.

23 But for any given drug, the actual metabolic  
24 regime can be very complicated, because as you see in the  
25 case of tasimelteon, you have different pathways going on

1 at the same time in competition with one another, or at  
2 least simultaneously. And if you affect one of those, you  
3 don't know what may happen on the other. We also won't  
4 know a priori, whether these metabolites themselves have  
5 biological activity.

6 So if, for example, it turned out that there's  
7 a -- this enzyme, 3A4, produced a metabolite, here labeled  
8 M14. But M14 is the same -- has the same kind of  
9 activity, the same degree of activity as the parent  
10 molecule tasimelteon. Then that -- that is not going to  
11 affect exposure to the drug, right, because it will have  
12 converted the drug into something else that just works the  
13 same way.

14 You can't know any of that up front. And it  
15 took a lot of work by Vanda to elucidate this. This  
16 figure is in this clinical study. It's also in the  
17 patent. It's figure 5 in the drug interaction patents.

18 And the practical significance of this, Vanda  
19 found, was that -- what they did was a clinical study  
20 where they co-administered tasimelteon with so-called  
21 CYP1A2 inhibitors. And the -- one of the examples of this  
22 is a drug called fluvoxamine, which is used for treating  
23 psychiatric conditions.

24 And when you co-administer tasimelteon with  
25 fluvoxamine, this is what happens. The green line is

1 tasimelteon by itself. That's what you want. And there  
2 we're seeing, Your Honor, that pulse that I mentioned  
3 earlier. Right. That's what will entrain, and then it  
4 goes away, so it's not going to create spillover.

5 If you give it with fluvoxamine, what you get  
6 is a much bigger peak and a much, much longer duration.  
7 And this is an invitation to spillover and undoing the  
8 phase shifting effects that are what you want for  
9 entrainment.

10 And in fact, if we look, for example, with the  
11 tasimelteon by itself, the peak exposure, the amount that  
12 the body would see, occurs at around half an hour. If we  
13 give it with fluvoxamine, you're still seeing that same  
14 level, which, we know, must be sufficient to phase shift  
15 at four hours. And so -- and you've got very significant  
16 amounts of it persisting after that.

17 So the reason to be concerned about this is it  
18 will undo the effects of tasimelteon and compromise  
19 entrainment.

20 Now, there's a problem in the other direction,  
21 too. Another thing that Vanda studied and found was that  
22 if you give tasimelteon concurrently with what's called a  
23 CYP3A4 inducer, you will create a problem going in the  
24 opposite direction. And here, the example of something  
25 that induces this enzyme is the -- a drug called rifampin.

1 It's also called rifampicin. Those are synonyms. That's  
2 an antibiotic.

3 And here, if you do those things, what happens  
4 now is that the pulse that we want is greatly reduced, and  
5 you compromise efficacy. The effect of having the two  
6 together is the body sees enormously less tasimelteon and  
7 there's a very good chance that will be insufficient for  
8 entrainment.

9 And the -- thirdly in this category, Vanda  
10 studied what is the effect of taking tasimelteon by itself  
11 versus taking it with food. And what they found here is  
12 that if you give it with food, you have -- the body sees  
13 the same amount of the drug, more or less, but it sees it  
14 over a longer time.

15 So in the language of the field, there's a  
16 lower maximum concentration, but a later time to hit the  
17 peak. And so graphically, this is what that will look  
18 like, right. Where, again, green is that same chart,  
19 that's the pulse that we want for entrainment.

20 Now, if we -- if the patient takes this at or  
21 around the time of eating, what will happen is, it will  
22 tend to reduce the height of the peak, the amount that the  
23 body is seeing, and spread it out over a longer time.  
24 Again, compromising the ability to entrain.

25 And so these are the incremental aspects of the



1 two drug interaction patents and the food-effect patent.

2 As far as infringement is concerned, we think  
3 that it's probably pretty straightforward. The patent  
4 says, the first one says if someone's taking a drug like  
5 fluvoxamine, discontinue it, and then treat with  
6 tasimelteon.

7 For the 3A4 patent, it says if someone is  
8 taking that, discontinue the rifampicin treatment and then  
9 treat with tasimelteon. The label -- and this language, I  
10 believe, was incorporated at the request of FDA -- says --  
11 tells the practitioner to avoid the use of tasimelteon in  
12 combination with fluvoxamine and to avoid it in  
13 combination with rifampin.

14 And so in terms of does the label encourage,  
15 recommend or promote, we think the answer is absolutely  
16 yes.

17 One thing I would point out -- because the  
18 claims are slightly, not slightly, are different. In the  
19 drug-drug interaction, there's no requirement for  
20 entrainment. So that issue about what does the label  
21 encourage, recommend or promote entrainment, even if  
22 defendants were correct on that, it would not help them on  
23 these patents.

24 And as to the food-effect patent, this is the  
25 one out of the five where infringement is conceded. If

1 the claim is valid, there's infringement. So the only  
2 issue for Your Honor is validity on this one. And the  
3 label says take it without food.

4 And I'll move to invalidity.

5 The key facts here, we think the evidence is  
6 going to show you need that pulse. And that's what is  
7 necessary for entrainment.

8 With respect to the '910 patent, the CYP3A4  
9 patent, there was no disclosure. I think this will be  
10 conceded. Simply not in the prior art, that tasimelteon  
11 was metabolized by this enzyme. And therefore, adjusting  
12 the treatment to -- because of this enzyme, right, is not  
13 something that, in our view, would even reach the starting  
14 line.

15 I think the defendants will argue, well, there  
16 were other similar drugs that were metabolized by this  
17 enzyme. But the system is so complicated, no one knew  
18 what was the effect of this enzyme, that we -- we think  
19 it's -- I mean, really a stretch, to be honest.

20 There is at least some suggestion that CYP1A2  
21 was involved in the metabolism of tasimelteon. That is  
22 based on in vitro data. And there's nothing to suggest  
23 that it actually had any -- that it would happen in a  
24 human being. I think we'll hear evidence about that,  
25 about to what extent, what would -- what could you tell

1 from the in vitro data. And there's no disclosure of the  
2 effect of food with administration of tasimelteon.

3 And so in our view, this isn't just a situation  
4 where you -- there's reason to avoid coadministration or  
5 taking it -- or eating it with -- having the drug with  
6 food because of the nature of how this drug works. And in  
7 order for it to do its job, you need that short sharp  
8 pulse. These issues are much more important here because  
9 they undermine the whole mechanism by which the drug  
10 operates.

11 With that -- there's also, Your Honor, a  
12 written description argument on the food effect patent, in  
13 which, if I understand it, the argument is the food effect  
14 patent, it tells you the effect of food, but it doesn't  
15 tell you why it matters. I will paraphrase, but that's  
16 what I understand the argument to be.

17 And the reason why, in our view, that's  
18 incorrect, Your Honor, is that the patent refers back to  
19 the earlier reissue patent and all of that data about  
20 entrainment and such like. And that tells you why the  
21 Tmax, the time to reach maximum exposure, is important and  
22 why that pulse matters.

23 And so we think it's not -- the incorporation,  
24 by reference, is certainly part of the written  
25 description. And if you look at that, everything is

1       there.

2               I'll move on to the last patent, so-called  
3       "impurities patent." And this is really in a different  
4       category of subject matter.

5               So here, as we saw, Vanda did a lot of work, I  
6       think we'll hear about this, on the manufacturing process.  
7       One of the things that they found in that, was that there  
8       were a number of impurities that were formed. And Vanda  
9       put in a lot of effort to actually identify those  
10      impurities by their chemical structure.

11              And the reason why that is important is, if you  
12      know the impurity that you're looking for and trying to  
13      control for, you can both have much greater assurance that  
14      you have accurately control for it and the product isn't  
15      containing something that will be harmful.

16              And also you can actually refine your process.  
17      For example, you might set new specifications for raw  
18      materials to prevent the formation of the impurity in the  
19      first place, if you understand the chemical mechanism by  
20      which it comes into being. And this, Vanda put a lot of  
21      work into this.

22              And here we see in this -- here's the claim.  
23      It has a lot of, perhaps, intimidating chemical  
24      terminology in it. But the way we break it down to say --  
25      it says: Composition of tasimelteon prepared by a

1 process, and it has two process steps here, creation  
2 steps. This is not, by any means, all of the tasimelteon  
3 process. But these are two of the key steps in making it.  
4 And I'll call one a reducing step and I'll call the other  
5 one a propionylating step. So it's --

6 **THE COURT:** What did you call it? A pro what?

7 **MR. GROOMBRIDGE:** Propionylating. And this  
8 is -- this is defining a particular family of chemical  
9 processes that would be used to make tasimelteon. There  
10 are other ways you could make tasimelteon, but this  
11 defines one of them.

12 If you're going to use this method, then -- the  
13 claim, then, defines five impurities. And it gives the  
14 chemical, the full chemical name for each one. But it  
15 calls them Impurities 5, 6, 1, 2, and 3. And the reason  
16 why four is not there, there was a four, and it has some  
17 historical significance, it's not relevant to this  
18 lawsuit.

19 And if we turn to Infringement here, one of the  
20 things that we see is that when Teva was seeking approval  
21 for its generic product -- this was in, I believe, around  
22 2017 or so -- they got what was called a complete response  
23 letter, which is what FDA sends you when it says, I can't  
24 approve your application because there are certain things  
25 that are not acceptable. And then you get to come back

1 and address their concerns.

2 And FDA called out Impurities 2, 3, 5 and 6.  
3 They reported this patent, which is the application that  
4 resulted in the patent we're litigating here. We don't  
5 know how they came up with this, but they did.

6 And they called out Impurities 2, 3, 5 and 6 to  
7 Teva. And they said, please control -- we know these can  
8 be made when you -- these can be created when you make  
9 tasimelteon. Either control these, explain to us that  
10 they're not going to be a problem or provide a  
11 justification for why you're not going to.

12 And not surprisingly, Teva responded. And they  
13 came back and said we are controlling for them. And  
14 Impurities 3 and 5, we can't actually separate these out,  
15 but we can assure you, FDA, that between the two of them,  
16 there won't be more than .1 percent by weight.

17 Impurity 2, we've got that one figured out.  
18 There won't be more than .1 percent by weight for that.  
19 And Impurities 1 and 6, they say, excluded by process  
20 difference. They say, knowing what this is, I can look at  
21 how it comes into being and I can look at my process and  
22 say we're not going to make this.

23 And so they came back and said, in answer to  
24 your question, FDA, there's not going to be a problem with  
25 Impurities 1, 2, 3, 5 and 6. And so we think the

1 infringement issue in this case has got to be pretty  
2 straightforward.

3 The exact same course of events played out,  
4 unbeknownst to Teva, with Apotex. FDA, likewise, gave  
5 them a complete response letter. Likewise said, we know  
6 Impurities 1, 2, 3, 5 and 6 can be created here, and they  
7 asked the same question. Please control for these.

8 **THE COURT:** Wait, wait. Why is this relevant?

9 **MR. GROOMBRIDGE:** Why is it relevant? Because  
10 it explains why Apotex responded to FDA saying, we have  
11 control for these impurities, and that's what creates  
12 infringement.

13 **THE COURT:** Okay.

14 **MR. GROOMBRIDGE:** It explains also why they are  
15 talking to FDA using the vocabulary of the Vanda patent.

16 **THE COURT:** All right.

17 **MR. GROOMBRIDGE:** And they say -- they, again,  
18 went through and said, we can control for all of these  
19 Impurity 1, 2, 3, 5, and 6. They are not going to be a  
20 problem in our process.

21 And so, again, there will be a noninfringement  
22 argument, but it doesn't relate to the presence of the  
23 impurities, it relates to the two process steps that I  
24 mentioned.

25 And on validity --

1           **THE COURT:** There's no distinction between  
2     Apotex and Teva; is that right? That is, I treat you all  
3     as one entity?

4           **MR. GROOMBRIDGE:** No. No, they both filed  
5     separate applications with FDA, each unknown to the other.

6           **THE COURT:** Okay.

7           **MR. GROOMBRIDGE:** And the FDA, it turned out,  
8     raised the same questions with both of them, and they then  
9     answered those. But neither one had visibility into what  
10    was going on with the other because this is all  
11    confidential.

12          **THE COURT:** Gotcha.

13          **MR. GROOMBRIDGE:** And the invalidity argument  
14    springs largely from the work that Bristol-Myers Squibb  
15    did. This is the patent that Bristol-Myers Squibb  
16    obtained that this is argued to be the prior art. It does  
17    disclose the process with those two process steps, it does  
18    not disclose any impurity information. And in our view,  
19    it doesn't give any motivation to someone to go chasing  
20    down these impurities.

21                There's an argument that the patent is invalid  
22    because BMS scientists should have been named as inventors  
23    on this. Again, we think there's no basis for that.  
24    There's no evidence that will show they had any  
25    appreciation. We think the evidence is going to show that



1 BMS -- as to Impurities 1, 2, 3, and 6, BMS never even  
2 knew they existed. And as to Impurity 5, they might have  
3 known it existed, but they got the structure wrong.

4 And certainly the -- I mentioned that the  
5 product that they were producing was not very clean. It  
6 could have impurity levels up to 3 percent, which is  
7 vastly inaccessible to them, of course.

8 So there's one other prior art reference, which  
9 is a Chinese patent application. Again, it discloses the  
10 process. But it has no mention of the impurities, and we  
11 think it doesn't give any -- there's no teaching here,  
12 there's no motivation to come up with this invention.

13 So that concludes my presentation, Your Honor.

14 And with that, I will yield to Mr. Rozendaal.

15 **THE COURT:** All right. Thank you.

16 **THE COURT:** Give me a second, please.

17 Are you presenting for both Teva and Apotex?

18 **MR. ROZENDAAL:** We will divide our time, Your  
19 Honor. I'm going to cover the invalidity issues, and my  
20 colleague, Mr. Coblentz, is going to cover the  
21 infringement issues.

22 **THE COURT:** Okay. Thanks.

23 **DEFENDANTS' OPENING STATEMENT**

24 **MR. ROZENDAAL:** May it please the Court.

25 What we've just heard from Mr. Groombridge is

1 quite a bit about what Vanda supposedly invented. But  
2 everyone agrees that Vanda did not invent tasimelteon, and  
3 everyone agrees that Vanda did not invent the use of  
4 tasimelteon to treat circadian rhythm disorders.

5 Bristol-Myers Squibb, often referred to as BMS,  
6 holds the patent on the tasimelteon molecule. It is the  
7 BMS '529 patent, and you will be hearing a lot more about  
8 it in the coming days.

9 The patent was issued in 1999. Claim 1 is on  
10 the tasimelteon molecule itself. But as can you see on  
11 DDX-1.2, the patent has claims directed toward treating  
12 sleep disorders and for treating circadian rhythm  
13 disorders in particular.

14 BMS granted an exclusive license to Vanda to  
15 commercialize tasimelteon. Thanks to that license, Vanda  
16 has enjoyed a monopoly on tasimelteon products in the  
17 United States for as long as they have been on the market.  
18 But that monopoly was too short for Vanda's liking. And  
19 so as that patent neared the end of its life, Vanda  
20 started cranking out follow-on patents to try to keep  
21 competitors off the market longer.

22 Although over the course of this lawsuit, Vanda  
23 has asserted 14 different patents against Teva and Apotex,  
24 now that we are at trial, we are down to five. Four of  
25 the patents are on methods of treating Non-24 using

1       tasimelteon, and the fifth is on highly purified  
2       tasimelteon made by a particular process.

3               But the evidence will show that Teva and Apotex  
4       don't infringe four of the five asserted claims, and it  
5       will also show that none of the five claims should have  
6       issued from the patent office because they do not  
7       represent any genuine invention.

8               There are two defendants in this case. I  
9       represent Teva Pharmaceuticals USA, and I'd like to  
10      acknowledge in the courtroom Teva's associate general  
11      counsel, Dr. Joseph Crystal.

12              As I said a moment ago, my cocounsel from  
13      Apotex Mr. Coblentz and I have divided up the issues for  
14      the opening statement. I'm going to address the  
15      invalidity of the patents, he's going to address why the  
16      patents are not infringed. And since I'm already standing  
17      up, I'm going to do invalidity for all five and then let  
18      him address infringement for all five rather than having  
19      us sort of bounce up and down, ping-pong style.

20              **THE COURT:** But he's going to do --

21              **MR. ROZENDAAL:** All four. Noninfringement for  
22      four of the five.

23              **THE COURT:** Including noninfringement for Teva?

24              **MR. ROZENDAAL:** Yes. So the arguments  
25      presented, I think, are going to be the same for both

1 defendants. It just turns out that they are two different  
2 products at issue.

3 **THE COURT:** Okay.

4 **MR. ROZENDAAL:** The story of tasimelteon really  
5 begins with the naturally occurring hormone melatonin,  
6 which is involved in regulating sleep/wake cycles, as Your  
7 Honor heard. Melatonin has been used to treat circadian  
8 rhythm disorders since the 1980s. It was discovered then  
9 that melatonin could shift the circadian phase. And by  
10 the year 2000, it had been shown that melatonin could  
11 entrain the circadian rhythm in patients suffering from  
12 Non-24.

13 But no one had an incentive to spend money to  
14 develop an FDA-approved version of melatonin because  
15 melatonin was a naturally occurring hormone that had been  
16 known for a very long time and, thus, didn't offer any  
17 meaningful prospect of patent protection.

18 And so these commercial issues created an  
19 incentive for researchers to try to find other drugs that  
20 had the potential to be patented but that would be  
21 melatonin receptor agonists, which is to say, drugs that  
22 would bind at the same receptors in the body as melatonin  
23 binds to and so would have similar effects on the body as  
24 melatonin. And that research led scientists at BMS to  
25 tasimelteon.

1           It turns out that tasimelteon was not the first  
2       drug in its class. There is another drug called  
3       ramelteon, which is a melatonin receptor agonist that came  
4       before tasimelteon. It's been approved by the FDA for  
5       treating insomnia, and it has a very similar chemical  
6       structure as to tasimelteon. You will be hearing more  
7       about the strong structural and functional similarities  
8       between the two drugs as the case proceeds.

9           To put Vanda's involvement with tasimelteon  
10      into perspective, we prepared a timeline. As early as  
11      1997, BMS had filed an investigational new drug  
12      application on tasimelteon with the FDA. And in that same  
13      year, it filed its patent application covering the  
14      tasimelteon compound which would protect exclusivity on  
15      the drug until at least 20 years after the filing date.

16           In 1999, the patent office granted the BMS  
17      patent application. It issued the '529 patent covering  
18      the tasimelteon compound. The drug is so old that the  
19      patent normally would have expired in December of 2017,  
20      but this one lasts longer. Title 35 USC Section 156  
21      allows a patent holder to extend the term of a patent to  
22      compensate for the time that it took the FDA to grant  
23      regulatory approval. And BMS and Vanda took advantage of  
24      that extension and got five years tacked on to the life of  
25      the patent so that Vanda will continue to enjoy its

1       tasimelteon monopoly until the '529 patent expires in  
2       December of this year.

3               As I said at the outset, the patent covers not  
4       only the compound itself, but methods of treating sleep  
5       disorders generally and circadian rhythm-related disorders  
6       in particular. And that means that by 1999, more than 20  
7       years ago, BMS had already synthesized tasimelteon,  
8       patented tasimelteon, and claimed the use of tasimelteon  
9       to treat circadian rhythm sleep disorders. As we are  
10      about to see, Vanda didn't even start working on  
11      tasimelteon until five years later, and it didn't apply  
12      for any of the patents that it's now asserting until 13  
13      years later.

14             Returning to our timeline, we can see that in  
15      2004, BMS entered into its exclusive license agreement  
16      with Vanda, that gave Vanda the rights to the '529 patent,  
17      to the FDA applications on tasimelteon, and importantly,  
18      to all of BMS's tasimelteon know-how.

19             Vanda filed a patent application on the use of  
20      tasimelteon to treat circadian rhythm disorders that was  
21      published in 2007. We refer to this as the "244  
22      Publication," and, as you will come to see over the course  
23      of trial, it discloses much of the material that Vanda is  
24      now claiming in the patents-in-suit.

25             Then Vanda ran clinical trials, and I'm going

1 to leave them off the timeline so as not to clutter it up,  
2 but there were clinical trials in insomnia patients. The  
3 protocols and the result of those trials are in the prior  
4 art. And then Vanda ran a clinical trial on Non-24  
5 patients. The results of the Non-24 trial were not yet  
6 public, but the protocol for the trial administering the  
7 drug to Non-24 patients was available on the  
8 clinicaltrials.gov website. And just to be --

9 **THE COURT:** How is that prior art if it is not  
10 publicly available?

11 **MR. ROZENDAAL:** No, it is publicly available on  
12 the website. Anyone who wants to look up the website can  
13 have access to it.

14 Our point is so -- the point that  
15 Mr. Groombridge made earlier was the protocol was known,  
16 the fact that the study was going on was known, but the  
17 results were not yet known; and we agree with that. Our  
18 point is that -- and I'll explain in a moment, but our  
19 point is that giving exactly the doses described in the  
20 current-by-product labels to people with Non-24 was  
21 something that had been done in the prior art -- or  
22 described in the prior art.

23 Finally, in 2012, Vanda filed patent  
24 applications directed to methods of using tasimelteon to  
25 treat patients suffering from Non-24. And these were the

1 earliest filing dates for the patents that are at issue in  
2 this case.

3 And the following year, Vanda filed its NDA, or  
4 New Drug Application, seeking approval for its own branded  
5 tasimelteon product which is now known as Hetlioz.

6 Only in 2014 did Vanda file the patent application  
7 that led to the '465 patent, which is the  
8 product-by-process patent that claims highly purified  
9 tasimelteon. And by that time, Chinese patent  
10 applications had already been published describing highly  
11 purified tasimelteon.

12 Vanda's 2012 and 2014 filing dates mean that  
13 Vanda was very late in seeking patent protection for using  
14 tasimelteon to treat Non-24 and also for purified --  
15 highly purified tasimelteon made by its claimed process.  
16 So the patents being asserted in this case are not valid  
17 and should not have been issued.

18 As I said before, there are five patents left  
19 in the case. And I'm going to start by focusing on the  
20 four method-of-treatment patents. I will leave the  
21 chemistry patent for the end.

22 To present our invalidity case on  
23 method-of-treatment patents, Defendants will call Dr.  
24 Jonathan Emens, who is an associate professor in the  
25 Department of Psychiatry and an assistant professor in the



1 Department of Medicine for Oregon Health and Science  
2 University. He's also deputy director of mental health  
3 for the VA Portland Healthcare System. He is a board  
4 certified sleep physician and psychiatrist with more than  
5 25 years of experience in researching sleep medicine and  
6 circadian physiology.

7           Going back to our patent overview, we can start  
8 with the reissue '604 patent on the far left, which we  
9 have labeled as the "entraining patent" because one  
10 salient claim limitation is entraining patients to a  
11 24-hour sleep/wake cycle. We intend to put on evidence  
12 showing that patent is invalid as obvious and anticipated.

13           We turn now to Claim 3 of the patent. You will  
14 see that Claim 3 depends from Claim 2, which depends from  
15 Claim 1. I'm not going to read the whole thing, but you  
16 can see from the highlighted portions that the claim  
17 requires: Entraining a patient suffering from Non-24 to a  
18 24-hour sleep/wake cycle by orally administering to the  
19 patient 20 milligrams of tasimelteon half an hour to one  
20 and a half hours before the target bedtime.

21           We expect to present three invalidity defenses  
22 for this claim. The first one is that the claim is  
23 obvious over the combination of the Lankford, Hack, and  
24 the 244 Publication.

25           And I'm just going to give you a brief preview

1 of the contents of those publications.

2 **THE COURT:** And just, again, it's Claim 3 we're  
3 talking about --

4 **MR. ROZENDAAL:** It's Claim 3 --

5 **THE COURT:** -- that you're limiting to?

6 **MR. ROZENDAAL:** Correct. So in order to show  
7 infringement of Claim 3, they need to show infringement of  
8 all the elements. And similarly for invalidity, we need  
9 to show all the elements of all three claims would have  
10 been obvious.

11 **THE COURT:** Okay.

12 **MR. ROZENDAAL:** Now, Lankford is an article  
13 published in a journal called Expert Opinion on  
14 Investigational Drugs in 2011, describing clinical trials  
15 involving tasimelteon. One of the dosing regimens used in  
16 the trials was 20 milligrams of tasimelteon 30 minutes  
17 before bedtime. Lankford discusses administering  
18 tasimelteon to totally blind patients with Non-24. It  
19 identifies tasimelteon as a melatonin receptor agonist and  
20 says: Therefore, that tasimelteon should be especially  
21 well-suited for treatment of circadian rhythm sleep  
22 disorders.

23 The Hack reference is an article in the Journal  
24 of Biological Rhythms from 2003. It summarizes prior work  
25 that had been done on melatonin, explaining that the phase

1 shifting effects of melatonin were first documented in  
2 humans in 1985; that melatonin had the ability to entrain  
3 circadian rhythms in totally blind people suffering from  
4 Non-24; and that melatonin should be given close to the  
5 desired bedtime for the treatment of Non-24.

6 The 244 Publication is a patent application  
7 filed by Vanda that was published in 2007. It's the same  
8 one that we saw in the timeline earlier and I said  
9 discloses much of what Vanda tried to patent later. It  
10 describes the mechanism of action of tasimelteon and  
11 states that: The engagement of the melatonin receptor in  
12 a part of the brain called the suprachiasmatic nucleus is  
13 believed to regulate circadian rhythms, including the  
14 sleep/wake cycle. It also describes the clinical trials  
15 involving tasimelteon and indicates that an oral dose of  
16 20 milligrams to 50 milligrams is effective in treating  
17 sleep disorders when administered about half an hour  
18 before bedtime.

19 So when you put together the information on  
20 tasimelteon from Lankford, with the literature on  
21 melatonin from Hack, in light of the 244 Publication that  
22 explains how the melatonin literature relates to  
23 tasimelteon, then the combination renders obvious and so  
24 invalidates Claim 3 of the RE604 patent.

25 Turning now to the second independent ground

1 for obviousness, we have a similar set of references  
2 exception that we remove Lankford and we substitute in the  
3 Hardeland reference in view of Hack and the 244  
4 Publication.

5 Hardeland is a review article published in  
6 Current Opinion on Investigational Drugs in 2009. Like  
7 Lankford, Hardeland describes the results of the  
8 tasimelteon clinical trials in insomnia. Hardeland says  
9 that: Tasimelteon was clearly effective in promoting both  
10 sleep onset and maintenance and that 20 milligrams a day  
11 was the most effective doses. Hardeland concludes that  
12 Tasimelteon is suitable for phase shifting the circadian  
13 clock and that it will presumably be useful in treating  
14 circadian rhythm sleep disorders.

15 Once again, when you put together the  
16 information about tasimelteon from Hardeland with the  
17 information about melatonin from Hack, plus the  
18 explanation of how the melatonin literature relates to  
19 tasimelteon in the 244 Publication, that combination also  
20 independently renders obvious and invalidates Claim 3 of  
21 the '604 patent.

22 Finally, we have an anticipation argument. And  
23 I think Mr. Groombridge referred to it as an obvious  
24 argument, so I'd like to make clear it is an anticipation  
25 argument. But it's a conditional argument, it depends on

1 the infringement case that Vanda puts on.

2 We expect Vanda to argue that the entrainment  
3 limitation of the '604 patent is the necessary result of  
4 administering tasimelteon according to the dosing regimen  
5 described in the Hetlioz label. Indeed, I think Vanda  
6 basically has to make that argument because the label  
7 doesn't say anything about entrainment, as you've heard  
8 from Mr. Groombridge.

9 But this creates a big problem for Vanda  
10 because Vanda had previously disclosed on the  
11 clinicaltrials.gov website for all the world to see as  
12 early as 2010 the very same administration protocol and  
13 regimen in Non-24 patients that is set forth in the  
14 Hetlioz label and also in the Teva and Apotex labels.

15 And so if you were to accept the premise that  
16 following that dosing regimen necessarily leads to  
17 entrainment, then the presence of the very same dosing  
18 regimen in the prior art necessarily would lead to  
19 entrainment as well, which inherently anticipates the  
20 claim here. And this is just an application of the  
21 principle that that which infringes if later anticipates  
22 if earlier than the patent.

23 **THE COURT:** Say that again.

24 **MR. ROZENDAAL:** So that's a patent lawyerism,  
25 Your Honor.

1           That which infringes if later, anticipates if  
2 earlier than the patent.

3           **THE COURT:** Right.

4           **MR. ROZENDAAL:** All right. Now we can turn to  
5 two similar patents, both of which deal with avoiding  
6 drug-drug interactions: Claim 14 of the '829 patent and  
7 Claim 4 of the '910 patent. The evidence will show that  
8 these claims are invalid as obvious in light of the prior  
9 art.

10           In addition to the testimony from Dr. Emens on  
11 these patents, you will hear from Dr. David Greenblatt who  
12 is a professor in the department of immunology at Tufts  
13 University School of Medicine. He has more than 40 years  
14 of experience in molecular and clinical pharmacology and  
15 drug-drug interactions.

16           Now first, a bit of background. There is a  
17 group of enzymes in the liver, predominantly in the liver,  
18 that plays an important role in metabolizing drugs. They  
19 are called the cytochrome P450 enzymes, or the C-Y-P, or  
20 CYP enzymes, for short. And each enzyme is given a  
21 three-part name in which the first number, as you can see,  
22 indicates a family; the second letter indicates a  
23 subfamily; and the last number indicates a specific  
24 enzyme.

25           And so, for example, the CYP1A2 enzyme is in

1 family CYP1, subfamily A, and it is enzyme Number 2.

2 As a matter of terminology, a drug metabolized  
3 by the CYP1A2 enzyme is called a CYP1A2 substrate. A drug  
4 that reduces the activity of the CYP1A2 enzyme would be a  
5 CYP1A2 inhibitor. And a drug that increases the activity  
6 of the CYP1A2 enzyme would be a CYP1A2 inducer.

7 And it turns out that you generally do not want  
8 to administer a CYP substrate with a strong CYP inhibitor  
9 or inducer. And the reason for that is shown in DDX-1.23.

10 Remember, the substrate -- in this case  
11 tasimelteon -- is metabolized or broken down by the CYP  
12 enzyme. And as you can see in the first row of the table,  
13 if you take the substrate together with a CYP inhibitor,  
14 not as much of the substrate will be broken down, and so  
15 the concentration of the substrate in the patient's blood  
16 plasma will increase. It's as if you've given the patient  
17 a higher dose of the drug.

18 That results in an enhanced effect on the body  
19 which could entail undesirable side effects.

20 Conversely, as shown in the second row of the  
21 table, if you take the substrate tasimelteon together with  
22 a CYP inducer, then more of the drug will be broken down,  
23 and so the concentration of the substrate and the blood  
24 plasma will decrease. It's as if you have given the  
25 patient a lower dose of the drug, and this leads to a

1 diminished effect on the body which could prevent the drug  
2 from being effective.

3 Because of these well-known interactions, it is  
4 obvious to skilled artisans to avoid administering drugs  
5 metabolized by given CYP enzyme together with a strong  
6 inhibitor or inducer of that enzyme.

7 And so with that background in place, we can  
8 take a look at Claim 14 of the '829 patent. Again, I'm  
9 not going to read the whole thing out loud, but it does  
10 require using tasimelteon to treat Non-24. But it has  
11 particular steps related to drug-drug interactions which  
12 are highlighted.

13 You need to start with a patient being treated  
14 with a strong CYP1A2 inhibitor, then discontinue treatment  
15 with a strong CYP1A2 inhibitor, and then treat the patient  
16 with 20 milligrams of tasimelteon daily.

17 As you can see on the left-hand side, we are  
18 using the same prior art combinations we went through  
19 before, Lankford, Hack, and the 244 Publication, except  
20 that we are adding in Hardeland this time. And the second  
21 independent obviousness combination that we are asserting  
22 is the one you saw before Hardeland, Hack, and the 244  
23 Publication. We don't have to add in Hardeland because  
24 it's already here, and you can infer from this that  
25 Hardeland has the key information that renders this claim



1 obvious.

2 The Hardeland reference describes tasimelteon  
3 clinical trials in insomnia patients, and as you can see  
4 on DDX-1.26, it says that: Tasimelteon is primarily  
5 metabolized by the CYP1A2 and other isoenzymes.

6 And then it goes on to say that:  
7 Coadministration of any drug that inhibits one of these  
8 isoenzymes should be regarded with caution.

9 That is an explicit warning in the prior art to  
10 avoid giving tasimelteon to a patient who is currently  
11 taking a CYP1A2 inhibitor, and it renders obvious the  
12 distinguishing feature of Claim 14 of the '829 patent.

13 We can now move on --

14 **THE COURT:** That's because CYP1A2 is an  
15 inhibitor.

16 **MR. ROZENDAAL:** CYP1A2 -- no, CYP1A2 is the  
17 enzyme that's doing the metabolism of the drug.

18 **THE COURT:** Right.

19 **MR. ROZENDAAL:** And so the instruction is one  
20 should not coadminister any drug that inhibits CYP1A2  
21 because it will affect the extent to which the drug is  
22 metabolized. So it would result -- as we saw earlier, it  
23 would -- the inhibition of the enzyme that does the  
24 metabolizing means that less of the drug would be broken  
25 down, you would end up with a higher amount of the drug in

1 the blood stream and could have side effects.

2 All right. This is a very -- and, obviously,  
3 Dr. Greenblatt is going to be able to explain this in  
4 great detail. But this is sort of a fundamental principle  
5 of drug-drug interactions. The CYP enzymes are all over  
6 the place, and avoiding coadministration of inhibitors or  
7 inducers together with drugs that are metabolized by these  
8 enzymes is a very basic principle of pharmaceuticals.

9 All right. If we go to the next patent, we  
10 have the '910 patent, which is very similar. Claim 4 is  
11 very similar, except that it involves a different enzyme,  
12 a different particular enzyme.

13 On the right side, we see the claim -- and,  
14 again, you need to start this time with the patient being  
15 treated with rifampicin. Rifampicin is an antibiotic  
16 that's used to treat very serious infections like  
17 tuberculosis and leprosy. Rifampicin is known to be an  
18 inducer of the CYP3A4 enzyme and, in fact, is perhaps the  
19 strongest known inducer of the CYP3A4 enzyme.

20 So the patent says to discontinue rifampicin  
21 treatment and then to treat the patient with tasimelteon.  
22 And why do you discontinue before treating with  
23 tasimelteon? The patent tells you: Thereby avoiding  
24 reduced exposure to tasimelteon caused by an induction of  
25 CYP3A4 by rifampicin.

1           So this is a situation where the rifampicin  
2       would increase the activity of the enzyme, it would  
3       metabolize more of the drug, and so, essentially, the  
4       drug -- the tasimelteon might not work if you take it  
5       together with the rifampicin.

6           So our prior art combinations for these are  
7       going to look familiar. We've got Lankford, Hack, and the  
8       244 Publication for using tasimelteon to treat Non-24. We  
9       add to that the Pandi-Perumal reference, and then  
10      similarly, we swap out Lankford for Hardeland; again, the  
11      same combination, Hardeland, Hack, 224 Publication for  
12      treating Non-24 with tasimelteon. Again, we add the  
13      Pandi-Perumal reference.

14          The Pandi-Perumal reference is a 2011 review  
15      article dealing with a drug called ramelteon, which, as I  
16      mentioned earlier, is a melatonin receptor agonist that  
17      came before tasimelteon, has a similar chemical structure  
18      and it says, in the top quoted portion of the slide, that  
19      the drug is metabolized by CYP1A2, CYP2C19 and CYP3A4  
20      enzymes. And in the bottom quoted portion on the slide it  
21      says: The CYP inducer rifampin -- and one of the few  
22      things that Mr. Groombridge and I agree on is that  
23      rifampin and rifampicin are the same thing -- CYP inducer  
24      rifampin or rifampicin has been shown to considerably  
25      decrease levels of losses in efficacy. This and other

1 strong up-regulators of relevant CYP enzymes should be  
2 avoided.

3 Defendants' expert, Dr. Greenblatt, will  
4 explain that due to the strong similarity in structure and  
5 activity of ramelteon and tasimelteon, skilled artisans  
6 would have understood from that disclosure about ramelteon  
7 that tasimelteon was also likely to interact with strong  
8 CYP3A4 inducers like rifampicin; meaning the  
9 coadministration of tasimelteon and rifampicin should be  
10 avoided, thus, rendering obvious the key distinguishing  
11 feature of Claim 4 of the '910 patent.

12 Because the prior art is so clear about the  
13 dangers of administering these drugs together with strong  
14 CYP inducers or inhibitors, the two claims from the  
15 drug-drug interaction patents are invalid.

16 And that brings us to the fourth and last of  
17 the method of treatment patents, Claim 5 of the '487  
18 patent which we've labeled here as the "without food"  
19 patent for reasons that will quickly become apparent. It  
20 is invalid for obviousness and for lack of written  
21 description.

22 Vanda is asserting Claim 5 of the patent which  
23 requires, essentially, administering 20 milligrams of  
24 tasimelteon to a Non-24 patient without food. The Court  
25 has construed "without food" to mean no food within 30

1 minutes before administration.

2 Again, these claims are obvious over the same  
3 prior art combinations we have seen a few times now.  
4 First Lankford, Hack, and the 244 Publication, and then we  
5 can take out Lankford and replace it with Hardeland in  
6 light of Hack, and 244.

7 Each of these prior art combinations teaches  
8 treating Non-24 by administering tasimelteon 30 minutes to  
9 an hour and a half before bedtime. And because most  
10 people don't eat dinner right before they go to bed, it  
11 would be obvious that if you were administering the drug  
12 shortly before bedtime, the administration is going to be  
13 without food as opposed to with food at least some of the  
14 time.

15 Furthermore, there are only two choices here.  
16 You can administer it with food or you can administer it  
17 without food. And when there are only two clear  
18 alternatives, either one of them would be obvious.

19 We also have a third invalidity argument which,  
20 like the anticipation argument for the reissue '604  
21 patent, is a conditional argument. And it depends on the  
22 position that Vanda takes on infringement.

23 We think that the claim requires nothing more  
24 than treating Non-24 by administering tasimelteon without  
25 food. But because that is so plainly obvious, Vanda might

1 try to argue that administering tasimelteon without food  
2 is more therapeutically effective than administering it  
3 with food, and that the food effect was not obvious.

4 Now, the claim, on its face, does not say  
5 anything about efficacy. But if the Court were to agree  
6 with Vanda, that the claim somehow incorporates a notion  
7 of improved efficacy, then the claim would be invalid, for  
8 lack of written description. And that is because the  
9 specification contains no information suggesting that  
10 administering without food is actually better at treating  
11 Non-24, than administration with food.

12 And so a skilled artisan reading the  
13 specification would not think that the inventors possessed  
14 an invention that includes improving efficacy in treating  
15 Non-24 by administering without food. And that is the  
16 separate reason why this patent is invalid.

17 All right. We're down to the last one.

18 The last one is the -- I'm going to leave the  
19 method of treatment patents and go to the one  
20 product-by-process claim, which is Claim 10 of the '465  
21 patent.

22 We intend to put on evidence showing that this  
23 patent is invalid as obvious, and due to the failure to  
24 name proper inventors.

25 Now, product-by-process claims are a little

1       quirky in that the requirements for establishing  
2       invalidity and infringement are not symmetrical. And  
3       that's because this type of claim was originally developed  
4       to deal with situations where you had done some reactions  
5       and created a new chemical compound, but you weren't sure  
6       exactly what the structure of the compound was, so you  
7       couldn't identify it by its molecular structure. And the  
8       only practical way to say what you had gotten was to  
9       describe the steps you took to create it.

10               All right. So as a result of that, to show  
11       infringement, it's going to be necessary to show that the  
12       proposed Teva and Apotex products are made using the  
13       claimed process steps, and that the resulting products  
14       meet the limitations of the rest of the claim.

15               But to show invalidity, Teva and Apotex just  
16       need to show that a product meeting the final description  
17       of the product, either existed or would have been obvious  
18       in light of the prior art, regardless of how it was made.

19               So one more time. To show infringement, they  
20       have to show that we used the patented process steps. To  
21       show invalidity, we just have to show that the product was  
22       obvious. We don't have to show it was made by those  
23       process steps.

24               **THE COURT:** Mr. Groombridge, do you agree with  
25       that?

1           **MR. GROOMBRIDGE:** I agree that, as a statement  
2 of product by process patent law, that's generally  
3 correct.

4           **THE COURT:** All right.

5           **MR. GROOMBRIDGE:** This claim is fairly  
6 complicated. And --

7           **THE COURT:** That's fine. But you agree with  
8 the principle, at least?

9           **MR. GROOMBRIDGE:** The principle.

10          **THE COURT:** The principle.

11          **MR. GROOMBRIDGE:** For a product-by-process  
12 claim limitation, which is part of this claim, I agree  
13 with that.

14          **THE COURT:** All right. Thank you.

15          **MR. ROZENDAAL:** I would point Your Honor for  
16 further comfort on this point --

17          **THE COURT:** No, he said he agrees with you.

18          **MR. ROZENDAAL:** Okay.

19               All right. So testimony on the invalidity of  
20 the '465 will come from Dr. Robert Perni, who's vice  
21 president of research and development at IM Therapeutics.  
22 Dr. Perni is a medicinal chemist with more than 30 years  
23 of experience in organic and medicinal chemistry and drug  
24 development.

25               The asserted --



1                   **THE COURT:** Is he in the room?

2                   **MR. ROZENDAAL:** I believe he is.

3                   **THE COURT:** Did you just testify in front of  
4 me?

5                   **DR. PERNI:** Excuse me?

6                   **THE COURT:** Did you testify in front of me  
7 recently?

8                   **DR. PERNI:** No, I have not.

9                   **MR. ROZENDAAL:** The asserted claim is directed  
10 to -- and it's a bear. But it's directed to a composition  
11 comprising tasimelteon prepared by a process comprising  
12 the steps of contacting and reacting one set of chemicals,  
13 then contacting and reacting a second set of chemicals to  
14 prepare tasimelteon, wherein the composition comprises  
15 0.15 weight percent or less of each a number of  
16 impurities.

17                   Making tasimelteon with low levels of  
18 impurities is an obvious thing to do, not least because  
19 the FDA guidelines require low levels of impurities.

20                   The FDA's purity requirements, which anyone  
21 wanting FDA approval for a drug would know about, rely on  
22 guidelines from an organization known as the ICH, which  
23 stands for International Council for Harmonisation.

24                   And actually, the full name is, the  
25 International Council for Harmonisation of Technical

1 Requirements for Pharmaceuticals for Human Use.

2 And as that name implies, the group's mission  
3 is to try to get different countries to harmonize their  
4 regulatory requirements for pharmaceuticals so that tests  
5 done to get regulatory approval in one country can also be  
6 used to get regulatory approval in other countries.

7 The FDA relies on ICH guidelines for various  
8 aspects of the drug approval process, including what we  
9 see here, ICH Q3A, the guideline on the threshold level of  
10 impurities, the highest of which, as you can see on the  
11 screen, is 0.15 percent.

12 And you will hear testimony from the named  
13 inventors of the '465 patent, that the 0.15 percent  
14 impurity level in the claim was chosen based on this  
15 guideline.

16 I do not think you will hear the inventor say  
17 that they invented a new way of making tasimelteon, or  
18 even a way to achieve new levels of purification for  
19 tasimelteon. What they did was to identify the chemical  
20 structure of the impurities that they found in their  
21 manufacturing process at low levels.

22 And to that we say, so what? Vanda rummaged  
23 through the dustbin of history and used routine tests to  
24 identify the chemical structures of impurities that had  
25 already been reduced to levels so low that nobody cared

1 what the structures of the impurities were. That is not  
2 activity inventive enough to be worthy of a patent.

3 And what is more, the way the claim is written,  
4 one doesn't even need to know the structure of the  
5 impurities to practice the claim. One just needs to have  
6 highly purified tasimelteon. As long as the total amount  
7 of all impurities is sufficiently low, the level of any  
8 given impurity will necessarily be below 0.15 percent.

9 We intend to present two prior art combinations  
10 that render this patent obvious. The first is the ICH Q3A  
11 guideline that we just looked at, which provides a strong  
12 incentive to keep the level of any given impurity below  
13 .15 percent, together with Chinese patent application  
14 No. '268, which was published in 2012. And it shows  
15 tasimelteon with impurity level of 99.6 percent.

16 Skilled artisans would have been motivated to  
17 combine it with the ICH guidelines, because anyone wanting  
18 to make a pharmaceutical product for FDA approval would  
19 look to the FDA-approved guidelines. And taken together,  
20 those references disclose highly purified tasimelteon with  
21 not more than .15 percent of any impurity.

22 For our second independent obvious combination,  
23 we take the same ICH Q3A guideline, but we substitute in  
24 the BMS '529 patent, the original patent on the  
25 tasimelteon compound from 1999, which I mentioned at the

1 very start of my opening statement today.

2 It shows that tasimelteon could be used for  
3 pharmaceutical products, including the treatment of  
4 circadian rhythm disorders. And, again, skilled artisans  
5 would have been motivated to combine it with the  
6 guidelines, because anyone wanting to make a  
7 pharmaceutical product for FDA approval would need to  
8 consider the applicable FDA guidelines.

9 Now, there's one other reason why the '465 patent is  
10 invalid, and that is that Vanda did not invent the claimed  
11 process for making tasimelteon. People at BMS did that.

12 You can see here on the timeline that we've put  
13 together, the priority date for the patent is all the way  
14 on the right on in 2014. One of the batches that BMS  
15 manufactured all the way back in February of 1998,  
16 16 years earlier, was tested and had total impurities of  
17 all kinds of just 0.15 percent. So there could not have  
18 been any individual impurity greater than 0.15 percent.

19 And according to Vanda's reading of the claims, BMS  
20 used the claim process to make its tasimelteon. But even  
21 though BMS used the claim process and met the claim purity  
22 levels, no BMS scientists are named as inventors on the  
23 '465 patent.

24 The omission of the people who actually developed the  
25 claimed process steps to achieve the claimed product and

1 then transferred that know-how to Vanda under the 2004  
2 license agreement, renders the patent invalid for improper  
3 inventorship under Sections 101 and 115.

4 Before leaving the topic of invalidity, I'd like to  
5 say a few words about secondary indicia of  
6 non-obviousness.

7 Once the Court has heard all the evidence, the Court  
8 will realize that the argument on secondary indicia from  
9 Vanda are flawed. But I'd like to focus on one particular  
10 flaw now, which is that the alleged secondary indicia have  
11 a nexus problem that is created by this '529 patent from  
12 BMS on the tasimelteon compound.

13 To illustrate the issue, let's look at DDX1.41. We  
14 can -- Vanda's going to say that they applied for their  
15 patents in 2012 or 2014, and that if these had -- and we  
16 will have pointed out, by the way, that there was an awful  
17 lot of prior art out there before that time.

18 And they're going to say, well, if it was really so  
19 obvious, how come nobody else did it first. The fact that  
20 it took so long to get these patents shows that they were  
21 really not obvious after all.

22 And that is an inference that doesn't hold up,  
23 because the BMS '529 patent is a blocking patent. It  
24 prevents anyone from using tasimelteon without BMS's  
25 permission. And the only company with a license from BMS

1 is Vanda.

2 So the fact that nobody else came out with the  
3 claimed invention sooner doesn't show that doing so wasn't  
4 obvious, it just shows that as long as the '529 patent is  
5 in force, no one else could develop any tasimelteon  
6 product regardless of how obvious it would be to do so.  
7 And that is a fundamental problem with Vanda's secondary  
8 indicia arguments.

9 So to sum up, the evidence will show that all of the  
10 asserted patents are invalid and should never have been  
11 issued. Vanda scrambled to come up with patents to try to  
12 prolong the life of its tasimelteon monopoly beyond the  
13 end of this year, but it came up short.

14 And with that, unless the Court has any questions, I  
15 will yield the floor to Mr. Coblentz.

16 **THE COURT:** All right. We'll take a break.  
17 Come back in ten minutes.

18 (Whereupon, a recess was taken.)

19 **MR. COBLENTZ:** May it please the Court, my name  
20 is Blake Coblentz. And I, along with our team,  
21 Cozen O'Connor, represent the Apotex entities in this  
22 case.

23 Now, you've heard Mr. Groombridge and  
24 Mr. Rozendaal, they discussed in great detail the asserted  
25 claims of the five patents-in-suit in this case.

1 Now, as for defendants' non-infringement case,  
2 I'm going to discuss the asserted claims of four of those  
3 patents. But before I get started in defendants' rebuttal  
4 arguments, I'd first like to discuss the infringement  
5 standard that controls here.

6 Now, Vanda does not allege that defendants  
7 directly infringed the method of treatment claims because  
8 defendants do not administer tasimelteon to patients.

9 So what are we talking about here? We're  
10 talking about whether defendants, Apotex and Teva, will  
11 indirectly infringe the method of treatment claims by  
12 inducing infringement --

13 **THE COURT:** Do me a favor, I'm good on this.  
14 There's a few things I'm good on.

15 **MR. COBLENTZ:** Okay. I got you. I got you.

16 Well, I will say, the one thing is, is that we  
17 did not hear contributory infringement from  
18 Mr. Groombridge.

19 **THE COURT:** He's not pursuing it.

20 **MR. COBLENTZ:** And it's our understanding  
21 they're not pursuing --

22 **THE COURT:** Well, let's double-check.

23 **MR. GROOMBRIDGE:** I think that's correct,  
24 Your Honor.

25 **THE COURT:** Okay. Good. So it's off.

1           **MR. COBLENTZ:** All right. Well, let's move on,  
2 then.

3           As Your Honor knows, I'm sure, as well, that  
4 when you look at induced infringement for the defendants,  
5 it's a matter of whether we encourage, recommend, promote  
6 or instruct a healthcare provider to use tasimelteon in a  
7 manner that is covered by the method of treatment claims.

8           Now, for companies like Apotex and Teva whose  
9 products are not yet marketed, the documents that are  
10 relevant to this inquiry is the defendants' labels. And  
11 the reason for that is --

12           **THE COURT:** We are good on that.

13           You agree with that?

14           **MR. COBLENTZ:** All right.

15           **MR. GROOMBRIDGE:** I absolutely agree with that.

16           **THE COURT:** All right. Let's go on. Next  
17 point.

18           **MR. COBLENTZ:** We'll move on. All right.  
19 So --

20           **THE COURT:** I knew you could do this in less  
21 than 13 hours.

22           **MR. COBLENTZ:** Okay. We can do it. All right.

23           **THE COURT:** All right.

24           **MR. COBLENTZ:** So I'm going to -- I'm going to  
25 skip to the positions that we're taking on infringement



1 here.

2 And for the purpose of Claim 3 of the reissue  
3 '604 patent, the evidence will show that defendants do not  
4 induce infringement for two separate reasons.

5 Now, neither Vanda's Hetlloz label or  
6 defendants' labels, which are substantially similar to  
7 Vanda's labels for the purposes of this infringement  
8 inquiry, neither one of them say anything about entraining  
9 a Non-24 patient to a 24-hour sleep/wake cycle. And they  
10 don't say anything about a Non-24 patient taking  
11 tasimelteon will sleep for approximately seven-to-nine  
12 hours.

13 Now, specifically looking at Claim 3 of the  
14 reissue '604 patent, we saw earlier it depends from  
15 Claim 1. And if we look at Claim 1 here, it requires a  
16 method of entraining a patient suffering from Non-24 to a  
17 24-hour sleep/wake cycle.

18 Now, stopping right there, we have to ask the  
19 question whether defendants' labels induce this limitation  
20 of the claim. And the evidence will show that defendants'  
21 labels do not include any of the words "entrain,"  
22 "entraining," "entrainment" or "synchronize" anywhere in  
23 their labels.

24 Now, if we look at Apotex's and Teva's drug  
25 labels, you will hear from our expert Ms. Jaskot.

1           **THE COURT:** Let me stop you. Is there any case  
2 law on this issue?

3           In other words, the label doesn't mention the  
4 condition or the word. And in an ANDA case, does that  
5 mean you win? Or, I mean, is there a case -- anybody  
6 address this in the Federal Circuit?

7           **MR. COBLENTZ:** I think there is some case law  
8 on this particular point. I think that in this particular  
9 case, when we're looking at whether defendants' labels  
10 say, you know, entrainment or anything other than --

11           **THE COURT:** It's undisputed. It doesn't say  
12 it.

13           **MR. COBLENTZ:** Right.

14           **THE COURT:** Right. What do the cases say?

15           **MR. COBLENTZ:** Well, I think the -- I mean, the  
16 cases support us here. And the cases will say that, you  
17 know, when it's not mentioned in the labels, the  
18 defendants, you know, aren't promoting or encouraging the  
19 infringing use.

20           **THE COURT:** So does it literally look for the  
21 word?

22           **MR. COBLENTZ:** Well, not necessarily look for  
23 the word, but anything that would -- that even, you know,  
24 comes close to that.

25           **THE COURT:** What's the best case you would cite

1 to me?

2 **MR. COBLENTZ:** I'd have to think -- I'd have to  
3 think about that.

4 **THE COURT:** Mr. Groombridge, you think the case  
5 law requires the word to be used?

6 **MR. GROOMBRIDGE:** Absolutely not, Your Honor.

7 **THE COURT:** What's the best case you can think  
8 of that supports your position?

9 **MR. GROOMBRIDGE:** Well, one that comes to mind  
10 is *AstraZeneca vs. Apotex*, which is the first of the  
11 "encourage, recommend and promote" cases. It's a Federal  
12 Circuit 2010, having gone back to look at it with respect  
13 to the word.

14 But the gravamen of that holding is that you  
15 look at whether the -- if people follow the label, will  
16 they be practicing the method. And in that case, it was  
17 found that they would. And that supported --

18 **THE COURT:** All right. But do you have any  
19 case where -- what I'm looking for is something more  
20 specifically the issue boiled down to the magic words were  
21 not used. You know, the condition or the activity that  
22 was -- that's identified specifically in the claim, it's  
23 not used, where that issue has been grappled with.

24 **MR. GROOMBRIDGE:** I am not aware of a case that  
25 grappled with the issue of a precise word.

1                   **THE COURT:** Okay. Are you?

2                   **MR. COBLENTZ:** I am not aware at this time.

3                   **THE COURT:** Okay. All right. Thank you.

4                   **MR. COBLENTZ:** Now, getting back, if we look at  
5 Apotex's and Teva's drug labels, you will hear from  
6 Ms. Jaskot that FDA regulations strictly require the same  
7 language that is present in Vanda's FDA-approved label for  
8 Hetlioz.

9                   Now, Ms. Jaskot, she's an expert in FDA  
10 regulations of branded and generic drug products. And she  
11 has more than 30 years of experience. And you will hear  
12 from Ms. Jaskot that the evidence will show there's good  
13 reason the words "entrain," "entraining," "synchronize" --  
14 there's good reason they do not appear in Vanda's labels  
15 or defendants' labels.

16                   Now, you're also going to hear from  
17 Dr. John Winkelman. He's the founder and chief of the  
18 sleep disorders clinical research program at Mass General  
19 Hospital. He's a professor at Harvard Medical School.  
20 He's got 30-plus years of experience diagnosing and  
21 treating sleep disorders.

22                   And he's going to tell you -- based on this  
23 30 years of experience, he will testify about how  
24 physicians who treat Non-24 interpret these labels for  
25 tasimelteon. And he will say why those labels do not

1       instruct a physician, such as himself, to use tasimelteon  
2       in a way that practices Claim 3 of the RE604 patent.

3               And Dr. Winkelman will specifically discuss  
4       that with medicine, there are drugs that can treat the  
5       symptoms of a condition, and there are those that can  
6       treat the cause of the condition.

7               Now, one example that you will hear  
8       Dr. Winkelman talk about is treatments for insomnia. And  
9       that's -- you can have a treatment of the underlying cause  
10      of the insomnia, which might be with a drug called  
11      fluvoxamine, which we'll hear a lot of about at this  
12      trial. And that will be treating the anxiety or the  
13      depression, which is -- would be the underlying cause of  
14      the insomnia.

15              On the other hand, there are drugs like Ambien  
16      that treat the symptoms of the insomnia, which is, you  
17      know, sleep deprivation. And the evidence will show that  
18      Vanda tried to get entrainment in the -- entrainment  
19      endpoints put in their label, and the FDA wouldn't let  
20      them do it.

21              Now, in the case of Hetlioz, the evidence will  
22      show that Vanda sought approval of its Hetlioz product  
23      from the FDA. It sought approval of two surrogate  
24      endpoints that Vanda informed the FDA would be measures of  
25      entrainment.

1 Now, those two endpoints that Vanda sought  
2 approval for, they are biomarkers.

3 Now, what is a biomarker? It's basically a  
4 biological molecule found in the blood, or other body  
5 fluids, that is assigned a specific process.

6 And in this case for Vanda, those biological  
7 molecules, that they informed the FDA were measures of  
8 entrainment, were a melatonin metabolite. Something in  
9 this case that you will see referred to as aMT6s, and  
10 cortisol.

11 And as you see in Slide 51 here, the FDA found  
12 that the entrainment biomarkers, that they could not --  
13 Vanda could not use those entrainment biomarkers in lieu  
14 of the primary clinical outcomes, which are the sleep  
15 outcomes.

16 And the evidence will show that the FDA  
17 repeatedly rejected Vanda's entrainment endpoints, and  
18 instead they accepted the clinical sleep endpoints that  
19 measured the improvement of the symptoms associated with  
20 Non-24.

21 Now, I know this is a little busy, but the  
22 point that we're trying to get across here is that Vanda  
23 tried to get FDA approval. When they tried to get FDA  
24 approval for these entrainment endpoints, they tried to  
25 get these entrainment measurements put in the label,

1 this -- these aMT6s and this cortisol.

2 But they failed in that effort. And the FDA  
3 did not allow Vanda to put that entrainment information in  
4 the actual approved label for Hetlioz. And because of  
5 this, the only clinical data that appears in Vanda's and  
6 defendants' labels is the clinical data that relates to  
7 improvement in sleep.

8 And as you see here, the only clinical data  
9 presented in the Hetlioz label is nighttime sleep time and  
10 daytime naptime, which are clinical sleep endpoints.  
11 They're not entrainment endpoints. And because of this,  
12 the evidence will show that Vanda's sales representatives  
13 are prohibited by FDA regulations from promoting Hetlioz  
14 for the treatment of Non-24 by entraining people.

15 Now, you'll hear from defendants' expert,  
16 Dr. Winkelman, and he'll testify that the assessment of  
17 the nighttime sleep time and daytime naptime that appears  
18 in the drug labels, that's directed to the symptomatic  
19 treatment of Non-24 patients, not the entrainment of the  
20 Non-24 patients.

21 Now, this is further supported by how Vanda  
22 references its endpoints in its own documents, like the  
23 clinical trial study documents, and the RE604 patent.

24 And if we look at the clinical study report  
25 from the -- what you've already heard about, was the SET

1 study, Vanda distinctly separated out the entrainment  
2 endpoints from the clinical symptomatic endpoints.

3 Now, in the primary objectives section of this  
4 clinical study report, it's -- Vanda specifically labeled  
5 entrainment as pertaining to the aMT6s rhythm. And that's  
6 that melatonin metabolite that we discussed earlier.

7 And then they go on to Point 2 in the primary  
8 objectives, and they mention this Non-24 clinical response  
9 scale, which is N24CRS. And that -- the evidence will  
10 show that is a sleep endpoint, not an entrainment  
11 endpoint.

12 And if we move to the secondary objectives in  
13 this clinical trial study, or report, what we see here is  
14 that for the entrainment endpoints, in the bullet below,  
15 they mention urinary cortisol, which we talked about  
16 earlier. But what they did not call as entrainment is the  
17 total nighttime sleep, which is labeled here as the  
18 LQNTST, or the daytime nap period, which is labeled here  
19 as the UQDTS. Those aren't labeled as entrainment  
20 endpoints here.

21 And the same is true for the reissue '604 patent.  
22 And if we look at the reissue '604 patent, which has been  
23 discussed a lot today, Vanda distinctly separated out the  
24 entrainment endpoints from the clinical symptomatic  
25 endpoints.



1 Now, we're looking at Table 1A and Table 1B  
2 from the RE604 patent here. And you see here that when  
3 looking at these specific endpoints, the entrainment  
4 parameters, aMT6s and the cortisol, are distinctly labeled  
5 "entrainment." Whereas the sleep parameters, the N24CRS  
6 and the LQNTST, UQDTSD, they're not labeled with that term  
7 "entrainment."

8 Now, to the extent that Vanda tries to go  
9 outside of its label to prove induced infringement here,  
10 it fares no better. Because as Dr. Winkelman will  
11 explain, the clinical trial data demonstrates that Non-24  
12 patients taking tasimelteon, that showed clinical  
13 symptomatic improvement --

14 **THE COURT:** I thought they can't go outside  
15 their label to prove inducement.

16 **MR. COBLENTZ:** And we agree, Your Honor.

17 **THE COURT:** Well, I think Mr. Groombridge has  
18 already just said that. So why are we talking about that?

19 **MR. COBLENTZ:** Well, we -- what we want to  
20 demonstrate here is that even if we looked at the data of  
21 the patent --

22 **THE COURT:** But why am I doing it if the law  
23 prohibits it?

24 **MR. COBLENTZ:** Well, we agree. We agree that  
25 we should --

1           **THE COURT:** So then, I'm not -- then why are we  
2       spending any time on it at all?

3           **MR. COBLENTZ:** Well, we just wanted to  
4       demonstrate that in the case of how tasimelteon treats a  
5       Non-24 patient, that it's not necessarily synonymous with  
6       entrainment. That because, what we see here is that -- we  
7       see here that double the patients had better sleep than  
8       they did entrainment.

9           And so in this particular case, entrainment is  
10      not synonymous with better sleep.

11          And so what you are going to see in the label  
12      is you're going to see the focus is specifically on the  
13      sleep parameters, this LQTST and this UQDTSD, which is the  
14      daytime sleep time -- or daytime sleep time and the  
15      nighttime sleep time.

16          And so the point here is is that that is not --  
17      those are not variables. Those are not parameters of  
18      entrainment. They are just parameters of sleep, and the  
19      patients can experience better sleep without actually  
20      being entrained, if that makes sense.

21          But I will move on.

22          Now, the second reason that defendants do not  
23      infringe Claim 3 of the RE604 patent is based on the  
24      requirement that the patient awakens at or near a target  
25      wake time following a daily sleep period of approximately

1 seven-to-nine hours.

2 Now, Vanda and defendants, we disagree about  
3 the "plain and ordinary" meaning of what this term means.  
4 Defendants maintain that this phrase means that the  
5 patient is mostly asleep for that seven-to-nine hours,  
6 allowing for times where a patient may awake during that  
7 period, for example, to maybe go to the bathroom or take a  
8 sip of water.

9 Now, if we look at Vanda's definition that was  
10 provided by Dr. Combs, there is this requirement for  
11 increased sleepiness. And this increased sleepiness leads  
12 to a result that a patient may never actually sleep during  
13 this seven- to nine-hour period of time. Increased  
14 sleepiness is not a part of Claim 3 or Claim 1 of the  
15 RE604 patent, and Dr. Winkelman is going to testify to  
16 this.

17 If you listen to his analysis, that under  
18 Vanda's definition, even if a patient does not sleep a  
19 wink during that seven-to-nine hours, but just experiences  
20 increased sleepiness, it would still meet the definition  
21 that Vanda has provided here.

22 But regardless of that, and regardless of which  
23 definition that is used here, the drug labels say nothing  
24 about a daily sleep period of seven-to-nine hours. The  
25 only information in the label that talks about the amount

1 of sleep is in the clinical trial section of the label.  
2 And there, patients on tasimelteon, they slept an average  
3 of 50 minutes longer on the 25 percent worst nights of  
4 sleep. So that's taking the patients from three hours and  
5 15 minutes of sleep to about four hours and five minutes  
6 of sleep.

7 And noticeably, I mean, it's not high math to  
8 understand that that is not equal to seven-to-nine hours  
9 of sleep. There is nothing in the label about how long  
10 patients set aside to sleep at night. There is nothing in  
11 the label about consolidating sleep to a seven- to  
12 nine-hour period. There's nothing in the label about  
13 waking up at a target wake time. There's nothing in the  
14 label about a goal or an aspiration that Non-24 patients  
15 that are taking tasimelteon may sleep seven-to-nine hours.

16 And for these reasons, Your Honor, there is no  
17 infringement of Claim 3 of the reissue '604 patent.

18 Now, the third reason defendants do not  
19 infringe relates to these two asserted patents that are  
20 involved in -- they are the drug-drug interaction patents;  
21 the Claim 14 of the '829 patent; Claim '910 -- or Claim 4  
22 of the '910 patent.

23 And these specific claims require three  
24 specific steps that are done in this order. And it's  
25 basically the patient has to be taking a strong CYP1A2

1 inhibitor or a CYP3A4 inducer, which the claim says is  
2 rifampin -- we've already heard that Rifampicin and  
3 rifampin are the same thing -- and then to discontinue the  
4 treatment with the strong CYP1A2 inhibitor or rifampicin,  
5 and then, and only then, administer tasimelteon.

6 Now, these claims further specify that the  
7 CYP1A2 inhibitors are the drugs fluvoxamine, verapamil,  
8 and Cipro. And the CYP3A4 inducer is rifampicin.

9 Now, these drugs treat very serious conditions.  
10 Fluvoxamine, for instance, it treats major depressive  
11 disorder and it also treats OCD. Verapamil treats cardiac  
12 conditions. Cipro treats bacterial infections. And  
13 rifampicin treats conditions like tuberculosis, leprosy,  
14 and Legionnaires' disease.

15 Apotex's and Teva's labels do not induce a  
16 prescriber or a patient to infringe these claims. The  
17 defendants' labels contain the same drug interaction  
18 information as the Hetlioz label. And all the labels say  
19 is to avoid coadministration -- coadministering a strong  
20 CYP1A2 inhibitor with tasimelteon or a strong CYP3A4  
21 inducer with rifampicin.

22 Importantly, the labels don't instruct  
23 prescribers on how to avoid that coadministration and  
24 certainly don't instruct prescribers to follow the  
25 specific ordered steps in the patent claims.

1 Now, there are a number of ways that a  
2 prescriber can follow the instructions on the label and  
3 not adhere to the ordered steps in the patent claims. The  
4 evidence in this case will show that it is -- it would be  
5 very, very unusual if you were to discontinue a patient on  
6 a medication that is treating serious conditions like OCD  
7 or a serious bacterial infection or a cardiac condition or  
8 tuberculosis just to put them on tasimelteon so that they  
9 could sleep better.

10 Now, the point we're making here is that  
11 instruction on an FDA label not to use tasimelteon  
12 together with another drug is not the same thing as an  
13 instruction to discontinue the other drug. And that's  
14 just as an instruction saying not to use a particular  
15 medicine while pregnant or nursing is not an instruction  
16 to discontinue being pregnant or discontinue being  
17 nursing.

18 In other words, defendants' labels are agnostic  
19 as to whether the physician takes the infringing route of  
20 discontinuing the other medicine and then administering  
21 tasimelteon, or the noninfringing route of continuing the  
22 medicine and refraining from administering tasimelteon.

23 And this is a distinction that is legally  
24 important because the case law is clear that the FDA label  
25 that describes or acknowledges an infringing use but does

1 not specifically encourage that use does not actively  
2 induce infringement. And the leading case on this is a  
3 case called *HZNP Medicines v Actavis Laboratories*, 940  
4 F.3d 680, and it was decided by the Federal Circuit in  
5 2019. And for these reasons, there is no infringement of  
6 Claim 14 of the '829 patent and Claim 4 of the '910  
7 patent.

8 Now, there was one additional  
9 method-of-treatment patent that was mentioned earlier that  
10 was the '487 patent. And Apotex and Teva have both  
11 stipulated to infringement of the only asserted claim of  
12 that patent which requires administering 20 milligrams of  
13 tasimelteon to a Non-24 patient without food. And our  
14 labels do, indeed, say to take the drug without food. So  
15 if that claim is held valid, we -- you know, Apotex and  
16 Teva would indirectly infringe it.

17 Now, when our labels encourage what the claims  
18 require, we admit it. But the exception -- but for the  
19 exception of that one claim, the evidence will show that  
20 defendants' labels do not actively induce infringement of  
21 the method of use claims.

22 Now, the last patent I want to discuss is a  
23 patent that's not like the rest of these, and I think  
24 you've heard of that multiple times. It's the '465  
25 patent. And it's not like the method-of-treatment

1 patents. But you heard Mr. Groombridge talk about the  
2 impurities. But what we're going to focus on for the  
3 noninfringement case for defendants is something  
4 different.

5 Now, this is a product-by-process patent that  
6 requires manufacturing tasimelteon by a specific process  
7 that requires contacting and reacting a carboxamide with  
8 both a reducing agent and an acid. Now importantly, the  
9 words to the claims itself requires that this be done in a  
10 single step.

11 Now, defendants' expert in organic and  
12 medicinal chemistry, Dr. Robert Perni, he has analyzed  
13 both Apotex's and Teva's methods producing tasimelteon.  
14 And in both cases, the carboxamide contacts the reducing  
15 agent and the carboxamide never contacts and reacts with  
16 the acid. Instead, the product of the reaction between  
17 the carboxamide and the reducing agent, it makes  
18 methanamine. And it's the methanamine that separately  
19 reacts with the acid to form the methanamine sulfate.  
20 Therefore, the series of steps used by Apotex and Teva,  
21 they do not infringe the claim as written.

22 Now, once you've heard all the evidence, we ask  
23 the Court to enter judgment that all the asserted claims,  
24 except for Claim 5 of the '487 patent, are not infringed  
25 and that all the asserted claims are invalid.



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1 Now, the last thing I want to say is that our  
2 client wished that they could be here today. She gave me  
3 permission to say this, but over the weekend her daughter  
4 was diagnosed with Covid so she had to stay home with her  
5 daughter. This is Ms. Kalinina. But she intended to be  
6 here today and cannot.

7 And the last thing I want to do is introduce  
8 our team from Cozen O'Connor. We have Aaron Lukas, Kerry  
9 McTigue, Barry Golob, Keri Schaubert, Derek Gretkowski,  
10 and Kaan Ekiner, and we look forward to presenting the  
11 evidence at trial.

12 **THE COURT:** Okay. Thank you. And tell your  
13 general counsel we understand, and send her daughter our  
14 best wishes.

15 All right. Ready to start the case?

16 **MR. GROOMBRIDGE:** Yes, Your Honor. Vanda calls  
17 as its first witness Dr. Mihael Polymeropoulos.

18 May we approach?

19 MIHAEL POLYMEROPOULOS, MD, having been called as a  
20 witness, being first affirmed or duly sworn under oath,  
21 testified as follows:

**DIRECT EXAMINATION**

22 **BY MR. GROOMBRIDGE:**

23 **Q.** Dr. Polymeropoulos, where are you from?

24 **A.** I'm originally from Greece.  
25

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1 Q. And how long have you lived in the United States?

2 A. About 38 years.

3 Q. Could you please tell us your role at Vanda.

4 A. I am the founder and chief executive officer of  
5 Vanda.

6 Q. And have you held that position essentially since the  
7 company was created?

8 A. Yes, since 2003.

9 Q. And what is your educational background?

10 A. My background is I studied medicine in Greece and  
11 moved to the US to do research at the National Institutes  
12 of Health, where I spent about 15 years studying molecular  
13 -- bacterial genetics, and then onto study the human  
14 genome in the human genome project, identifying diseases,  
15 developing genetic markers, including forensic markers.

16 And from there, I moved on to work at Novartis.

17 Q. Let me just pause for a moment.

18 Before you went -- what year did you go to Novartis?

19 A. That was '98.

20 Q. And, Dr. Polymeropoulos, have you been a practicing  
21 physician in the United States?

22 A. Yes, I have. I studied psychiatry and practiced  
23 psychiatry up until 2003.

24 Q. And did you, in that capacity, actually see patients?

25 A. Yes.

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1     **Q.**   Now, have you published the results of research,  
2     scientific research that you have done?

3     **A.**   Yes, extensively with a little over 150 publications  
4     and peer-reviewed journals.

5     **Q.**   How did it come about that you left the National  
6     Institutes of Health and went to Novartis?

7     **A.**   In the years of about '97, '98, I led a team. We  
8     discovered the first gene for Parkinson disease. And the  
9     reaction I got from patients --

10           **THE COURT:** What? The first what for Parkinson  
11     disease?

12           **THE WITNESS:** Gene.

13           **THE COURT:** The first gene for Parkinson  
14     disease.

15     **BY MR. GROOMBRIDGE:**

16     **Q.**   While we are on that point, since His Honor asked,  
17     did that attract any attention in the wider world?

18     **A.**   Absolutely. In fact, so many years later, it has  
19     changed the way people think about Parkinson disease and  
20     the molecule identified which is now the target of  
21     extensive development, drug efforts.

22     **Q.**   Now, anyway, please continue telling us how it came  
23     about that you joined Novartis.

24     **A.**   Yeah. I was working with a number of families that  
25     contributed to this research. And while they were excited

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1 about the discovery, also they were very anxious to see  
2 how they can translate that in their families. And the  
3 opportunity came up to go to Novartis and build the  
4 department of pharmacogenetics and be involved much closer  
5 now to being in products to patients.

6 **Q.** Just so the record is clear, what is Novartis?

7 **A.** Novartis is a international pharmaceutical company  
8 based in Switzerland.

9 **Q.** How long did you remain with that company?

10 **A.** I remained there for five years.

11 **Q.** Just in very general terms, what did you do while you  
12 were there?

13 **A.** My title was vice president, head of  
14 pharmacogenetics, and I build an international group  
15 studying the genetic factors that affect drug response  
16 across the entire portfolio of products from Novartis.

17 **Q.** And how did it come about that you left Novartis?

18 **A.** Well, it was after September 11, 2001, that I made a  
19 decision I wanted to build a US-based company and advance  
20 my interest and drive development on my own.

21 **Q.** And did that eventually lead to the creation of  
22 Vanda?

23 **A.** Correct, in 2003.

24 **Q.** And how did Vanda come into being?

25 **A.** I cofounded the company with a venture capital firm

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1 based in Princeton. And we tried to identify potential  
2 compounds that may have failed in the hands of other large  
3 pharmaceutical companies and bring them in and try to  
4 identify uses for them.

5 **Q.** And has that continued to be Vanda's business model  
6 up until today?

7 **A.** Correct.

8 **Q.** And how did it come about that Vanda got involved  
9 with development work on the molecule tasimelteon?

10 **A.** One of our colleagues in the venture capital firm  
11 knew of the business development team on the Bristol-Myers  
12 Squibb. And we contacted them to see whether they have  
13 any compounds that they would be interested in licensing,  
14 and one of them was what is now known as tasimelteon.

15 **Q.** How did the interaction with Bristol-Myers Squibb  
16 proceed after that initial contact?

17 **A.** Yeah. We signed a confidentiality nondisclosure  
18 agreement to get access to some documents that would allow  
19 us due diligence to decide whether or not we'll proceed  
20 with a licensing discussion.

21 **Q.** And having signed that confidentiality agreement,  
22 what did Vanda do, if anything, to evaluate tasimelteon?

23 **A.** It was, what we call it, a due diligence in a number  
24 of critical documents, including the investigators  
25 brochure, clinical trial data, and evaluation of the stage

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1 of manufacturing development.

2 **Q.** And let me ask you, please, to turn in the white  
3 binder in front of you to the first document, which should  
4 be Plaintiff's Trial Exhibit 613.

5 Do you have that?

6 **A.** Yes.

7 **Q.** Do you recognize this?

8 **A.** I do.

9 **Q.** What is it?

10 **A.** That is the BMS investigative brochure, or BMS  
11 21-4778, which is now known as tasimelteon.

12 **Q.** Was this a document that was provided to you by BMS,  
13 as you described just now?

14 **A.** Correct.

15 **MR. GROOMBRIDGE:** Your Honor, we offer  
16 Plaintiff's Exhibit 613 into evidence.

17 **MR. MILLIKEN:** No objection, Your Honor.

18 **THE COURT:** It's admitted.

19 (Plaintiff's Exhibit 613 admitted into  
20 evidence.)

21 **MR. GROOMBRIDGE:** Could you put the first page  
22 of that exhibit up on the screen, please. And let's  
23 enlarge the title.

24 **BY MR. GROOMBRIDGE:**

25 **Q.** Dr. Polymeropoulos, what is the reference to BMS

1 21-4778?

2 **A.** That is a molecule known as tasimelteon.

3 **Q.** Was that the code name by which BMS referred to  
4 tasimelteon?

5 **A.** Correct.

6 **Q.** What does it mean that it was melatonin agonist?

7 **A.** That it could bind to melatonin receptors and  
8 increase their activities.

9 **Q.** Could you tell us what is a melatonin receptor?

10 **A.** A melatonin receptor is a receptor in the cell  
11 surface of many cells. It belongs in a family of the  
12 G-protein-coupled receptors.

13 **Q.** And in the body, is that where naturally occurring  
14 melatonin will attach?

15 **A.** It will attach to initiate the downstream signals.

16 **Q.** Would those downstream signals be relevant in any way  
17 to sleep?

18 **A.** Correct. We know that melatonin plays a role in  
19 regulation of circadian rhythms. And one of the most  
20 well-known circadian rhythms is the sleep/wake cycle.

21 **Q.** Now, this document is called an Investigator  
22 Brochure.

23 What is that in the context of pharmaceutical drug  
24 development?

25 **A.** In the course of conducting clinical studies, the

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1 data up to that point are presented in summary form to the  
2 investigators who conduct the study to familiarize them  
3 with a drug.

4 **Q.** Now I'd like to turn, please, to Page 13 of this  
5 document. And just for clarity, Dr. Polymeropoulos, I  
6 will be referring to the trial exhibit page numbers that  
7 are in the center bottom of the document.

8 **A.** Okay.

9 **Q.** Do you have Page 13?

10 **A.** Yes.

11 **Q.** Now, I see there there's some handwritten notations.  
12 Do you know who made those?

13 **A.** I did.

14 **Q.** And what was the context in which you were annotating  
15 this document?

16 **A.** Actually, I recall this being a printed material that  
17 I had received during my visit in Princeton under this  
18 confidentiality nondisclosure agreement. I was reading  
19 this on the train back to Washington, D.C., taking notes.

20 **Q.** And, for example --

21 **MR. GROOMBRIDGE:** Let's enlarge the first two  
22 lines under "Pharmacology," Mr. Weir, please. Not  
23 "pharmacy," "pharmacology," lower in the page.

24 **BY MR. GROOMBRIDGE:**

25 **Q.** Why did you circle MEL1A and MEL1B receptors?



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1     **A.** To identify which receptors does this compound have  
2     affinity for. And MEL1A and MEL1B are two of the  
3     receptors that the endogenous melatonin is known to  
4     activate.

5                 **MR. GROOMBRIDGE:** Let's turn, please, to  
6     Page 19 of the document. And Mr. Weir, please enlarge the  
7     second part of the paragraph in the middle of the page.

8     **BY MR. GROOMBRIDGE:**

9     **Q.** Dr. Polymeropoulos, did you draw the boxes around the  
10    phrases "acute phase shifting" and "chronic  
11    reentrainment"?

12    **A.** I did.

13    **Q.** And why?

14    **A.** It was of interest that in the experiment described  
15    above with BMS 21-4778, the advanced, it appeared that the  
16    compound was active in acute phase shifting and what we  
17    discuss as chronic reentrainment, and suggesting that they  
18    have circadian capabilities.

19    **Q.** What did you understand "acute phase shifting" to  
20    mean?

21    **A.** A shift to the circadian phase after a single or  
22    acute administration.

23    **Q.** And is "acute" contrasted with "chronic," meaning  
24    repeated?

25    **A.** Correct.

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1 Q. What do you understand "chronic reentrainment" to  
2 mean in the context of these experiments?

3 A. Most probably learned an ability of a chronic  
4 circadian effect in a rat model where entrainment was  
5 compromised but then -- that's it.

6 Q. And what is the difference between reentrainment  
7 versus just plain entrainment in this context?

8 A. Well, I'm not sure exactly what they mean by  
9 "reentrainment," and different people may use it  
10 differently.

11 Entrainment in the context of a 24-hour rhythm is  
12 entrainment to the desired 24-hour rhythm. So if someone  
13 has a rhythm that is longer than 24, would like to entrain  
14 them to 24.

15 MR. GROOMBRIDGE: Let me ask you to turn,  
16 please, to Page 47 of this document. And Mr. Weir, when  
17 you get there, please enlarge the three lines at the top.

18 BY MR. GROOMBRIDGE:

19 Q. Do you see there, Dr. Polymeropoulos, that you put an  
20 annotation on this sentence that reads BMS 21-4778 was  
21 primarily metabolized by CYP1A2, 1A2, 2D6 and 2C9.

22 Why was that of interest to you?

23 A. It was another set of complexity that would have to  
24 be investigated with these four systems named as  
25 potentially metabolizing 21-4778.

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1 Q. Why would that be a source of complexity.

2 A. Because we would need to understand the relative  
3 contribution, if any, of each one of them in the human,  
4 and by that the effect that inhibitors and inducers of  
5 these enzymes may effect the levels of the drug that could  
6 affect the effect of the drug.

7 Q. When you say "relative contribution," please explain  
8 what you mean.

9 A. Yeah. They're noting four different systems with a  
10 potential of metabolizing. We don't know if 90 percent of  
11 the drug is metabolized through 1A1 and then the rest of  
12 the 10 percent through the other systems.

13 And that is critical because, for example, there are  
14 four systems, and if one of them could create capacity of  
15 25 percent, the worst-case scenario would be a 25 percent  
16 alteration if one of the systems was perturbed. So we  
17 would have to understand the relative contribution of each  
18 one of them.

19 Q. And I notice in the next sentence, it lists various  
20 enzymes that, according to this sentence, did not  
21 metabolize BMS 21-4778.

22 Do you see that?

23 A. I do.

24 Q. And do you see that the last one listed is 3A4?

25 A. Correct.

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1       **Q.**    Is that CYP3A4?

2       **A.**    Yes.

3       **Q.**    With the knowledge we have now, is it correct that  
4       the statement is wrong?

5       **A.**    Yes. That is an incorrect statement.

6       **Q.**    Now, let's turn, please, to the next document which  
7       should be JTX-064.

8           Let me ask you, do you recognize that?

9       **A.**    I do.

10      **Q.**    What is it?

11      **A.**    That is the clinical study report for BMS study  
12      CN116004 that was a primary insomnia in the elderly.

13      **Q.**    Was this likewise a document that you received from  
14      BMS as part of the due diligence?

15      **A.**    Correct.

16           **MR. GROOMBRIDGE:** Your Honor, we offer JTX-64  
17      into evidence.

18           **MR. MILLIKEN:** No, objection, Your Honor.

19           **THE COURT:** It's admitted.

20           (JTX-64 is admitted into evidence.)

21           **MR. GROOMBRIDGE:** Let's put that up on the  
22      screen, please, Mr. Weir. And just enlarge the  
23      highlights, please -- enlarge the title, please.

24      **BY MR. GROOMBRIDGE:**

25      **Q.**    And what is this referring to, Dr. Polymeropoulos?

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1     **A.**    It refers to the design of the study,  
2     placebo-controlled double-blind study of three fixed doses  
3     of compound in the treatment of elderly patients with  
4     insomnia.

5     **Q.**    And what was the hypothesis underlying this clinical  
6     trial, as you understand it?

7     **A.**    The hypothesis was that insomnia that is quite often  
8     seen in the elderly may have a circadian causation, and a  
9     circadian regulator could have a therapeutic effect.

10    **Q.**    What was the outcome of this clinical trial by BMS?

11    **A.**    The trial failed to prove this hypothesis.

12    **Q.**    And in the due diligence as a result of that, did you  
13    find out what had happened next with BMS after this trial  
14    failed?

15    **A.**    BMS lost interest in the compound after this failure  
16    and stopped development.

17    **Q.**    Did Vanda enter into an agreement with BMS with  
18    respect to tasimelteon?

19    **A.**    Vanda did, yes.

20    **Q.**    And what were the salient terms of that agreement?

21    **A.**    It was a small upfront payment of half a million  
22    dollars. And in exchange, we'll get all the documents  
23    that were prepared and information up until this point,  
24    and then Vanda would have obligations for certain  
25    milestones as the compound moved along in development and

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1 commercialization.

2 **Q.** And when you characterize the upfront payment as  
3 small, why is that?

4 **A.** It was a payment reflective of the lack of interest  
5 or BMS's understanding of value within this program. And  
6 the half a million was really a token for their paperwork  
7 and licensing documents.

8 **Q.** Now, let me ask you to turn to the next document in  
9 the binder, which should be JTX-111.

10 Do you have that?

11 **A.** Yes.

12 **Q.** And do you recognize this?

13 **A.** I do.

14 **Q.** What is it?

15 **A.** This is a summary of an internal Vanda assessment of  
16 BMS 14478 before licensing in order to make an internal  
17 decision whether to license or not.

18 **Q.** And did you participate in that decision-making  
19 process?

20 **A.** Yes, I did.

21 **MR. GROOMBRIDGE:** Your Honor, we offer JTX-111  
22 into evidence.

23 **MR. MILLIKEN:** No objection.

24 **THE COURT:** All right. It's admitted.

25 (JTX-111 is admitted into evidence.)

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1 **BY MR. GROOMBRIDGE:**

2 **Q.** Let me ask you to turn, please, Doctor, to Page 10 of  
3 this document. And let's start with --

4 **MR. GROOMBRIDGE:** Please, let's enlarge the  
5 section headed Indications.

6 **BY MR. GROOMBRIDGE:**

7 **Q.** Dr. Polymeropoulos, it says there: Evidence from  
8 clinical studies suggests that -- let's just call it  
9 tasimelteon -- has chronobiotic properties in humans as  
10 well as animals.

11 What does chronobiotic mean in this context?

12 **A.** Chronobiotic refers to what I talked about earlier,  
13 circadian capabilities; meaning that it may be able to  
14 adjust the circadian rhythm.

15 **Q.** And do you see there, there's also a reference to  
16 something called DLMO.

17 What is that?

18 **A.** That is a reference to dim light melatonin onset, and  
19 it indicates the timing of the initial increase of  
20 nighttime melatonin.

21 **Q.** And similarly, what does "Tmin" mean in this context?

22 **A.** It refers to the time minimum.

23 **MR. GROOMBRIDGE:** Now, let's take that down,  
24 please, Mr. Weir, and let's highlight the next paragraph  
25 headed 4.1.

1 **BY MR. GROOMBRIDGE:**

2 **Q.** And what does CRSD stand for here?

3 **A.** It stands for circadian rhythm sleep disorders.

4 **Q.** And you see it says there are seven recognized  
5 subtypes.

6 Would you agree with that?

7 **A.** Correct.

8 **Q.** And one of those is something called "shiftwork sleep  
9 disorder" or SWSD.

10 What is that?

11 **A.** It is a sleep disorder that occurs due to the change  
12 in sleep schedules due to shiftwork.

13 **Q.** And another one is jetlag type. What is that in the  
14 context of circadian rhythm disorders?

15 **A.** It's the sleep-wake disorder caused by the rapid  
16 transition across time zones, like jet travel.

17 **Q.** And I notice that the condition known as Non-24 is  
18 not called out in the list here.

19 Is there a reason for that?

20 **A.** The reason that we saw it separately is because it is  
21 the one caused by endogenous lesions and does not have an  
22 external stimulus to cause it.

23 **Q.** And is that by contrast to all the other ones?

24 **A.** Correct.

25 **Q.** Now, it states there, beginning on the fifth line:



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1 Vanda plans to initially develop BMS 214778 for the  
2 treatment of SWSD and jetlag-type sleep disorder.

3 Was that a correct statement?

4 **A.** That is correct.

5 **Q.** Why did you pick those two as the ones that you  
6 wanted to target, those two conditions?

7 **A.** Because we believed that the study of them may be  
8 less confounded, in that we knew the stimulus that can  
9 cause the sleep disorder and, therefore, have a more  
10 straightforward clinical study program.

11 **Q.** And just so we all understand, what does "confounded"  
12 mean in this context that you just used it?

13 **A.** Our interest, when we study a drug in a clinical  
14 trial setting, is to confirm that there are no factors, or  
15 few factors, in the program itself that may lead to a  
16 false-negative result. That the drug actually works. But  
17 we could not see this effect because of other factors that  
18 we could not control.

19 **Q.** And there's a reference there to something called a  
20 "proof-of-concept trial."

21 What is that?

22 **A.** It is the indication that we want to do an early  
23 experiment to understand whether, in this case, it goes on  
24 to say we will assess the amount of phase shift achievable  
25 with BMS-214778 treatment.

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1 We did not know at the time whether a phase shift can  
2 be achieved, and what would the size, the amount of the  
3 phase shift would be.

4 **Q.** Just for clarity of the record, does the abbreviation  
5 "POC" in this document refer to a proof-of-concept trial?

6 **A.** Correct.

7 **Q.** And when did you find out whether tasimelteon was  
8 capable of phase shifting?

9 **A.** We found out after the -- after in licensing and  
10 after conducting the first SET study. The study, we refer  
11 to it as Study 2101.

12 **Q.** And did Vanda initiate a development program of  
13 tasimelteon for the treatment of jetlag and shiftwork  
14 disorders?

15 **A.** We initiated development plans, but they never came  
16 to fruition at that time. We have since developed a  
17 program for jetlag.

18 **Q.** Looking at the work that was going on in the  
19 immediate years after you licensed tasimelteon, about how  
20 many years did you spend looking at jetlag and shiftwork?

21 **A.** The whole concept was probably -- took between 2004  
22 to 2009, about five years.

23 **Q.** Now, let me --

24 **MR. GROOMBRIDGE:** Let's, please, Mr. Weir, take  
25 that down and please put up Paragraph 4.2, which begins on

Page 10 and carries over to the top of Page 11.

**BY MR. GROOMBRIDGE:**

**Q.** Now, Dr. Polymeropoulos, did you already tell us why Non-24 sleep-wake disorder was called out separately from all the other ones?

**A.** Because it referred to a chronic condition without an external stimulus that will perturb the circadian rhythm.

**Q.** And I note here, this begins by saying: Vanda will potentially develop BMS-214778 for Non-24-hour sleep-wake disorder.

Why was that potential, as opposed to a definite decision?

**A.** Yeah. We were not certain whether we could undertake this development, understanding the potential complexity of both in recruiting for such a study, but also for protocol that will be successful.

**Q.** So what would be the potential complexity with regard to recruitment for such a study?

**A.** To go back to confounding. One way to reduce confounding would be to select a population where the reason for Non-24-hour sleep-wake disorder could be surmised, and that was -- excuse me, the totally blind, where they lack the light stimulus that is necessary for daily entrainment.

But we knew it would be difficult to identify

1 sufficient number of totally blind individuals for two  
2 reasons. One, that the condition of total blindness is  
3 rare in itself. And second, the awareness at that time of  
4 Non-24, even amongst the blind community was extremely  
5 low.

6 **Q.** What would be the complexity what was involved in  
7 designing the protocol for a trial to investigate the use  
8 of tasimelteon for Non-24?

9 **A.** First, we knew that a goal, the goal, of a successful  
10 treatment Non-24-hour sleep-wake disorder that would be  
11 accepted by experts would have been the demonstration of  
12 entrainment of the 24-hour circadian rhythm.

13 In order to demonstrate that, you would have to have  
14 an elaborate way of serial collection of samples. And in  
15 this case, it would end up being continuous collection for  
16 24 hours of urine over long periods of time, and that can  
17 last several weeks to months, and do this with totally  
18 blind people. Clearly, you know, a very difficult  
19 undertaking.

20 And then was that the clinical endpoints suffered  
21 from a different confounding factor. And that is, in a  
22 placebo-controlled study, would be expected that some, or  
23 even more than some, placebo patients will show, in the  
24 period of evaluation, an improvement of sleep.

25 So just that clinical outcome would be confounded as

1 well.

2 **Q.** Now, there's a reference in the -- in this paragraph  
3 to a second proof of concept to investigate the phase  
4 entraining properties of BMS-214778.

5 My question is: Why would you need a second one if  
6 you'd already did a proof of concept of phase shifting?

7 **A.** The proof of concept that I discussed earlier  
8 referred to the ability to phase shift and the amount of  
9 phase shifting, and actually, specifically to phase  
10 advance to an earlier time. That's what we would have  
11 learned from the first proof of concept.

12 **Q.** And going on, the document states with respect to the  
13 second proof of concept, the trial will investigate  
14 whether BMS-214778 entrains circadian rhythm and improves  
15 sleep quality in this population.

16 My question, Dr. Polymeropoulos, was: When did Vanda  
17 learn that tasimelteon could, indeed, entrain patients  
18 suffering from Non-24?

19 **A.** Only after the completion of the SET and RESET  
20 studies.

21 **Q.** Approximately what year was that?

22 **A.** I believe that was around 2012.

23 **MR. GROOMBRIDGE:** Now, let's take that down,  
24 please, Mr. Weir. One final thing to cover on this. Can  
25 you enlarge the heading Development Risks and

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1 Manufacturing, please.

2 **BY MR. GROOMBRIDGE:**

3 **Q.** And, Doctor, why was manufacturing called out as a  
4 potential development risk?

5 **A.** If we -- well, as we're planning to undertake a full  
6 development program, and eventually, if successful,  
7 commercialize the drug, we would have to develop a  
8 reliable manufacturing synthesis process, scale it up, and  
9 develop it so that it will have commercial level grade.

10 **Q.** And why would that propose a potential risk for the  
11 company?

12 **A.** Because it could be possible because it has been  
13 other compounds that we cannot scale up. You may not be  
14 able to remove impurities in a way that it is viable and  
15 cost-effective.

16 **Q.** And what was the state of the manufacturing process  
17 that you inherited from Bristol-Myers Squibb when you did  
18 this deal?

19 **A.** I'm not a manufacturing expert. But the panel of  
20 experts we put together described it as a very early  
21 glassware-level synthesis; meaning that they had been able  
22 to produce milligram quantities of the drug that will not  
23 be sufficient to carry on a clinical program.

24 **Q.** Now, let's move on. I'd like to look at the next  
25 document, please, which should be defendants' Trial

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1 Exhibit 25. Let me know if you have that.

2 And, Dr. Polymeropoulos, is this a paper published in  
3 a scientific or medical journal on which you are one of  
4 the authors?

5 **A.** Which exhibit is that?

6 **Q.** Should be the next one in the binder, and it should  
7 be defendants' Exhibit 25.

8 **A.** Yes.

9 **THE COURT:** It's not the next one in my binder.  
10 I have PTX- 816. That's what he has.

11 **MR. ROZENDAAL:** I don't have any defense  
12 exhibits in this notebook.

13 **MR. GROOMBRIDGE:** Don't know why that would be,  
14 Your Honor. Perhaps, we have a mistake here. 816 is the  
15 next one?

16 **THE COURT:** PTX- 816 is what we have next.

17 **MR. GROOMBRIDGE:** I don't even know what that  
18 is.

19 **THE COURT:** It's the Lancet.

20 **MR. GROOMBRIDGE:** Let me ask you this. Let's  
21 put that up, if it is what I think it is.

22 Yes. It's the same document. This is just by  
23 plaintiff's number, I think. Right?

24 **THE COURT:** Okay. Well, that's not the first  
25 page. There is a cover page, the Lancet.

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1           **MR. GROOMBRIDGE:** Oh, I now understand.

2           **THE COURT:** But I think it's the same thing.

3           **MR. GROOMBRIDGE:** Your Honor, just to avoid any  
4 confusion. Think that it's the same paper. The  
5 plaintiff's version has the cover of the journal and the  
6 defendants' one doesn't.

7           **THE COURT:** Well, it's also different, though.

8           For instance, that page there, it doesn't look  
9 the same. I mean, the title looks the same, but the list  
10 of folks on the left when you're showing on the screen,  
11 I'm going to guess, appear on the right in the one we  
12 have. I will guess they are two iterations of the same  
13 thing.

14           **MR. GROOMBRIDGE:** Fair enough. Let's work with  
15 816, then, if that's okay. And I'll just go with this  
16 one.

17           **BY MR. GROOMBRIDGE:**

18           **Q.** Doctor, this is a paper published in the Journal of  
19 the Lancet, in which you're one of the authors.

20           **A.** Correct.

21           **MR. GROOMBRIDGE:** Your Honor, we offer  
22 Plaintiff's Exhibit 816 into evidence.

23           **MR. MILLIKEN:** No objection.

24           **THE COURT:** All right. It's admitted.

25           **MR. GROOMBRIDGE:** And apologize for the



1 confusion there.

2 (Plaintiff's Exhibit 816 is admitted into evidence.)

3 **BY MR. GROOMBRIDGE:**

4 **Q.** What year was this published, Doctor?

5 **A.** That was published in February 2009.

6 **MR. GROOMBRIDGE:** And let's, please, Mr. Weir,  
7 put the first page of the article up on the screen and the  
8 title. And the author's, too. Yes, please. Thank you.

9 **BY MR. GROOMBRIDGE:**

10 **Q.** Now, who is the first listed author on this?

11 **A.** It's Dr. Rajaratnam.

12 **Q.** And is this a paper that is often referred to as the  
13 "Rajaratnam Paper"?

14 **A.** Correct.

15 **Q.** What was your role in the work that's reported here?

16 **A.** I collaborated in the design, execution and analysis  
17 of the data, and authoring the paper.

18 **Q.** And does this report the results of a clinical trial?

19 **A.** Correct.

20 **Q.** And -- or two clinical trials.

21 What was the subject of those trials?

22 **A.** Both trials examined the effect of tasimelteon, which  
23 is also referenced with Vanda here VEC-162, its affects in  
24 a model of a five-hour phase advance, or the equivalent of  
25 traveling from New York to London.

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1 Q. And how was that simulated, traveling from New York  
2 to London?

3 A. That was simulated by, in the first study, bringing  
4 people in a time isolation unit at Harvard University, and  
5 asking them to initiate sleep five hours before their  
6 regular bedtime.

7 And the second study was done with more patients.  
8 Again, the same model in a sleep lab.

9 Q. And I notice that the title refers to Transient  
10 Insomnia. What is that in the context, for example,  
11 jetlag?

12 A. It is known that the insomnia produced by jetlag is  
13 transient in nature. That means it will dissipate over a  
14 few days.

15 Q. Is that what -- why it's transient?

16 A. Correct.

17 Q. And by contrast, what is chronic insomnia?

18 A. Chronic is a type of insomnia that will not dissipate  
19 over time.

20 Q. Did Vanda also ultimately do work on the tasimelteon  
21 for chronic insomnia?

22 A. Correct.

23 Q. And what, if anything, became of that?

24 A. That study aimed to identify whether tasimelteon can  
25 treat patients with chronic insomnia. And the results of

1 that study were mixed, in that it helped with insomnia in  
2 the first part of the night, sleep onset, but it did not  
3 help with sleep maintenance, which was in contrast to what  
4 is described, actually, in this paper, with the second  
5 largest study.

6 **Q.** And did Vanda ever develop tasimelteon for use in  
7 treating chronic insomnia?

8 **A.** We did not.

9 **Q.** And let me ask you to look at one thing in this  
10 paper. If we go to -- let's go to Page 7, please.

11 **MR. GROOMBRIDGE:** And, Mr. Weir, I'd like the  
12 text that begins at the last two lines of the right-hand  
13 column on Page 7 and carries over to the next two lines,  
14 under the table on the next page.

15 **BY MR. GROOMBRIDGE:**

16 **Q.** Doctor, you see there it says in the sentence that  
17 begins "although": Only tasimelteon 100 milligrams  
18 shifted DLMO 25 percent significantly earlier than did  
19 placebo.

20 What does that mean?

21 **A.** That means that out of the four tasimelteon doses  
22 tested, 10 milligrams, 20 milligrams, 50 milligrams,  
23 100 milligrams, the one that caused a phase shift, in this  
24 case a phase advance which was larger and statistically  
25 significantly different than placebo, was only the highest

1 dose of 100 milligrams.

2 **Q.** The work that's reported in this paper, Exhibit  
3 Plaintiff's 816, did that tell you whether tasimelteon  
4 could or could not entrain patients suffering from Non-24?

5 **A.** No, it did not. That was not the question that was  
6 being asked in this periodical.

7 **Q.** And by the way, I see that this was published in a  
8 journal called "The Lancet."

9 What is that?

10 **A.** It's one of the premier medical journals.

11 **Q.** Let me ask you now, please, to turn to the next item.  
12 Unless I have made another mistake, this should be -- my  
13 colleague passes me a question that might be important  
14 that I forgot.

15 In the paper we were just looking at, the Rajaratnam  
16 Paper, is it correct that the subjects in the trial were  
17 not blind people, they were sighted people?

18 **A.** Correct. They were all sighted, healthy volunteers  
19 with no history of a sleep disorder of circadian rhythm  
20 sleep disorder.

21 **Q.** Now, let's look at Plaintiff's Exhibit 2. And is  
22 this another scientific paper from the Lancet journal on  
23 which you are also an author?

24 **A.** Correct.

25 **MR. GROOMBRIDGE:** We offer Plaintiff's

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Exhibit 2.

**MR. MILLIKEN:** No objection, Your Honor.

**THE COURT:** All right. It's admitted.

**MR. GROOMBRIDGE:** Please put that up, Mr. Weir.

Please enlarge the title.

(Plaintiff's Exhibit 2 is admitted into evidence.)

**BY MR. GROOMBRIDGE:**

**Q.** And, Dr. Polymeropoulos, this refers to something called "SET" and "RESET."

What are they?

**A.** They are the acronyms for the two randomized studies in blind patients with Non-24-hour sleep-wake disorder.

**Q.** When were they conducted?

**A.** They were conducted, including the design, sometime between 2010 and '12.

**Q.** And what did Vanda learn from those two studies?

**A.** We learned that tasimelteon, as administered, was able to entrain the circadian rhythm of blind people with Non-24. And from the RESET study, that it can maintain that entrainment.

**Q.** And was this the first time that those effects had been shown?

**A.** That is correct.

**Q.** Let me ask you to turn, please, to Page 3.

**MR. GROOMBRIDGE:** And, Mr. Weir, let's enlarge

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1 the text on the right-hand side at the top.

2 **BY MR. GROOMBRIDGE:**

3 **Q.** Do you see there, Doctor, it says: Patients were  
4 asked to take a study drug every 24 hours at a fixed clock  
5 time, one hour before the target bedtime.

6 Was that important?

7 **A.** Very important.

8 **Q.** Why?

9 **A.** Because we wanted to make sure that it was not a --  
10 that variable administration may have unpredictable and  
11 detrimental results to the effect of the drug.

12 **Q.** Why would a variable time of administration  
13 potentially have such results?

14 **A.** We had hypothesized, and based on the  
15 proof-of-concept phase shifting work, that what we maybe  
16 needed is a short pulse of the drug and a quick  
17 dissipation, but that had to be done at the exact  
18 relationship with the circadian time. Circadian time  
19 being the endogenous time of the circadian rhythm.

20 **Q.** Why is it that the pulse would have to be there at a  
21 fixed time relative to the circadian rhythm?

22 **A.** If given too early, may be ineffective. If given too  
23 late, it may actually allow the drug the body's exposed  
24 to, to instead of phase advancing, phase delaying. And in  
25 terms of entrainment, would be unpredictable, which way it

1 would go.

2 **Q.** Now, in the same text, the next sentence says:  
3 Patients were asked to maintain a self-selected --  
4 self-selected fixed nine-hour sleep opportunity and target  
5 bedtime starting between 2100 hours and 0100 hours.

6 And it continues.

7 Was that important?

8 **A.** That was extremely important. Not only were trying  
9 to fix the start time to be with a reasonable flexibility,  
10 but they had to agree to be between 9:00 and 1:00 a.m.

11 But very importantly, they would need to allot  
12 nine hours of sleep opportunity.

13 **Q.** What does sleep opportunity mean in this context?

14 **A.** It's the time you would set aside that you will  
15 attempt to sleep within that period. It is the allotted  
16 time for that sleep period.

17 **Q.** And was it expected that the patients would actually  
18 be asleep throughout that nine-hour period?

19 **A.** No. That is what the study was examining. There was  
20 no hypothesis how long they were going to sleep during  
21 that time period.

22 **Q.** Let's go to Page 7, please.

23 **MR. GROOMBRIDGE:** And, Mr. Weir, can you  
24 enlarge the bottom figure there. If you put it on the  
25 screen, I will indicate -- maybe I have another mistake.

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1 I'm looking at PTX- 2, Page 7. Maybe go to the next page.  
2 That one. Please enlarge the part of the figure here.

3 **BY MR. GROOMBRIDGE:**

4 **Q.** What are relooking at here, Doctor?

5 **A.** We're looking --

6 **THE COURT:** Hold on. Just so the record is  
7 clear, when I look at this later on, I've got it at  
8 Page 8.

9 **MR. GROOMBRIDGE:** Yes. I'm not sure why,  
10 Your Honor. But, again, I seem to have some --

11 **THE COURT:** That's okay. But let's just make  
12 it clear so when we read the transcript later on, it's  
13 Page 8.

14 **MR. GROOMBRIDGE:** Yes.

15 **THE COURT:** All right. Sounds good.

16 **MR. GROOMBRIDGE:** Maybe, Mr. Weir, let's just  
17 enlarge the part of the figure that's in the upper left  
18 corner so we can make it bigger.

19 **BY MR. GROOMBRIDGE:**

20 **Q.** What are we looking at here, Doctor?

21 **A.** This is a graphical display of a person's nighttime  
22 and daytime sleep. And it is plotted in parallel for ease  
23 of examination.

24 So you -- the vertical line with the numbers that  
25 refer today, minus 56, 28 and zero, are the days



1 proceeding randomization, or the screening period. And  
2 after that, zero through 84 and beyond are its day during  
3 treatment.

4 The dotted line on the first -- exactly at the Y axis  
5 and the next tick mark, indicates the nine-hour sleep  
6 opportunity. And the white area between the next dotted  
7 lines is the daytime period.

8 Q. So if we look at this, did this patient start  
9 receiving tasimelteon on day zero?

10 A. Correct.

11 Q. And prior to that, did the horizontal lines show when  
12 this patient was recording sleep each day?

13 A. Yes. Which was done with a daily diary every day.

14 Q. Does this show entrainment?

15 A. Sorry. I cannot see where you are pointing.

16 Q. Does the --

17 A. Yes. So the top of the figure with the red asterisk  
18 shows the non-entrainment, the Non-24, where you see the  
19 asterisk progressing from day to day. And in the bottom  
20 of the figure, you see the asterisks, all of them, are  
21 aligned at the same time of the day, which is entrainment.

22 Q. What does the red asterisk stand for?

23 A. It is the calculated peak of the sulfatoxymelatonin,  
24 melatonin in the urine.

25 Q. And does this -- can you see from this how much of

1 the nine-hour sleep opportunity window the patient  
2 actually slept each day?

3 **A.** Well, on the top of the figure, you see that there  
4 are a lot of white parts; meaning they slept very little  
5 those nights. But some nights when they were temporarily  
6 at the right phase, they slept more.

7 When you start at zero going down, there's a lot more  
8 black filling, which means they slept more time. And I  
9 would guess, knowing that this is a nine-hour, it ranged  
10 from six, seven-to-nine hours. Some nights were lower,  
11 some nights were higher.

12 **Q.** What is the reason why the length of sleep at night  
13 would improve following the administration of tasimelteon?

14 **A.** Because of the entrainment. Once the endogenous  
15 circadian rhythm is entrained, then the sleep-wake cycle,  
16 which derives from the entrainment circadian rhythm, will  
17 obey.

18 **THE COURT:** Thank you, Doctor. Can you hold  
19 for a second?

20 You know, I guess, I think this takes me a long  
21 time. I'm having a hard time reading this graph. All  
22 right. This doesn't make sense to me.

23 **MR. GROOMBRIDGE:** Can I take another run at it,  
24 Your Honor?

25 **THE COURT:** Let me just ask. I mean, maybe

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1 it's faster. So I've got -- what's the left axis? It  
2 represents number of days, right? Drug, start taking on  
3 day zero?

4 **MR. GROOMBRIDGE:** Correct.

5 **THE COURT:** Okay. And this is for one patient?

6 **MR. GROOMBRIDGE:** This is a single patient.

7 **THE COURT:** Right. Single patient.

8 So the red asterisk, you say, indicates  
9 entrainment?

10 **THE WITNESS:** Indicates where your endogenous  
11 rhythm is at, and it's supposed to be at the same time  
12 every day. But instead, you see the progression was days  
13 go down from the top, the asterisk moves to the right,  
14 meaning it's progressing day after day. And since we are  
15 measuring, I believe, awake intervals, you see within that  
16 week, it's moved that much.

17 **THE COURT:** Okay.

18 **THE WITNESS:** But after drug, on zero then the  
19 asterisk no longer moved. That is the definition of  
20 "entrainment."

21 **THE COURT:** Right. And the left axis, or the X  
22 axis, represents time, right?

23 **THE WITNESS:** The X axis, it is actually the  
24 day. It is double-plotted; meaning the left figure and  
25 right figure is the same. It is actually hours of the

1 day, so 24-hour.

2 And the dotted vertical defines the nine-hours  
3 sleep figure, and therefore, the rest of it -- the rest of  
4 it is the 15 hours remaining in the day.

5 And you can see on the top during the  
6 screening, there are a lot of sleep episodes during the  
7 white part. These are the daytime naps, which coincide  
8 with the time when the melatonin rhythm was traveling  
9 through the day.

10 **THE COURT:** All right. Just why is it  
11 double-plotted?

12 **THE WITNESS:** The experts in the field decided  
13 it's easier to see the pattern when you double-plot.

14 **THE COURT:** It literally is, it's just a  
15 replica.

16 **THE WITNESS:** Correct. Exactly.

17 **THE COURT:** It is exactly the same.

18 **THE WITNESS:** Yeah.

19 **THE COURT:** Okay. All right. That's fine.  
20 Thank you.

21 **THE WITNESS:** Mr. Groombridge, the D panel has  
22 a point that may be useful to make.

23 **BY MR. GROOMBRIDGE:**

24 **Q.** Well, since you obviously -- I ask the questions.  
25 But let's look at the D panel.

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1           What is shown is -- is this a set -- a different  
2       patient that we're looking at?

3       **A.**    A different patient on placebo. And in this case, we  
4       see that during the screening and during randomization,  
5       the red asterisks travel; meaning the person is not  
6       entrained. And you could not have gathered that just  
7       looking at the sleep. The sleep looks like the black  
8       lines filling the night.

9       **Q.**    Thank you.

10           Now, in the interest of time, I'm going to move  
11       along. Can I ask you to turn to the next item, which I  
12       hope will be Plaintiff's Trial Exhibit 187.

13           All right. Is this a document that you're familiar  
14       with?

15       **A.**    Yes, I am.

16       **Q.**    What is it?

17       **A.**    It is a clinical pharmacology study looking at the  
18       interaction between tasimelteon in combination with a  
19       CYP1A2 inhibitor fluvoxamine.

20           **MR. GROOMBRIDGE:** Your Honor, we offer  
21       Plaintiff's Exhibit 187.

22           **MR. MILLIKEN:** No objection.

23           **THE COURT:** All right. It's admitted.

24           **MR. GROOMBRIDGE:** Mr. Weir, please put that up.

25           (PTX-187 is admitted into evidence.)

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**BY MR. GROOMBRIDGE:**

**Q.** Doctor, why was Vanda interested in studying potential interaction between tasimelteon and fluvoxamine?

**A.** We wanted to understand whether or not fluvoxamine and tasimelteon does not -- would affect the levels and kinetics of tasimelteon.

**Q.** And what is fluvoxamine, by the way?

**A.** Fluvoxamine is in a class of antidepressant drugs that is indicated, among other things, for the treatment of obsessive compulsive disorder.

**Q.** Let me ask you, please, to turn to Page 53.

**MR. GROOMBRIDGE:** And, Mr. Weir, please enlarge the diagram that appears there.

**BY MR. GROOMBRIDGE:**

**Q.** What is this, Dr. Polymeropoulos?

**A.** It is a map of the metabolic pathway for tasimelteon in humans.

**Q.** And what does it mean to be a map of the metabolic pathway?

**A.** It gives us a schematic, what happens when tasimelteon is administered and how the body disposes of it.

**Q.** And did Vanda do the work that resulted in this, the creation of this map?

**A.** Yes, we did.

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1 Q. And how did you do that in broad terms?

2 A. It was done with a combination of in vitro and  
3 in vivo experiments.

4 Q. And why would you be interested in doing the work to  
5 create this metabolic map?

6 A. It was critical, especially for this drug in this  
7 indication where timing and shape of exposure is critical  
8 to understand precisely how the different metabolic  
9 systems may affect the exposure of a person to  
10 tasimelteon.

11 Q. I think you said that in this application, time and  
12 exposure were critical. Why?

13 A. The -- not only the timing of administration of  
14 tasimelteon is important to achieve and maintain  
15 entrainment for Non-24, but also the amount of drug in the  
16 bloodstream after the administration, and that can be  
17 affected by the various disposition pathways.

18 Q. What would be the relationship between the various  
19 disposition pathways and the amount of blood in the  
20 drug -- amount of drug in the bloodstream?

21 A. Well, that would have to be examined. That's  
22 being -- experiments are aiming to understand what percent  
23 of the drug may be metabolized from each one of the types.  
24 But also importantly, if one of them is perturbed, do the  
25 others make up for it, and what would be the eventual

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1 effect in exposure.

2 **Q.** Does knowing that a particular enzyme is involved in  
3 the metabolism of a drug tell you whether that will be  
4 important or not important in the human body?

5 **A.** It does not.

6 **Q.** Why not?

7 **A.** For example, if the pathway up on the left is  
8 blocked, it may make no difference in the amount of the  
9 drug. If the other arrows pick up the overflow, you will  
10 not know.

11 **Q.** And let me ask you, please, to turn to Page 56 and  
12 look at Figure 3 there.

13 And no need to pull that up.

14 Dr. Polymeropoulos, did we -- did you ask us to  
15 prepare a color-coded version of this?

16 **A.** Yes. Thank you.

17 **MR. GROOMBRIDGE:** Mr. Weir, please put up  
18 PDX- 3.1. Go to 3.2, please.

19 **BY MR. GROOMBRIDGE:**

20 **Q.** And is this that color-coded version, Doctor, of that  
21 PDX 3.2?

22 **A.** Correct.

23 **Q.** What's the green curve in this?

24 **A.** The green is the measurement of tasimelteon in the  
25 bloodstream when administered alone.



1 Q. And what's the yellow curve?

2 A. Tasimelteon exposure when tasimelteon is  
3 coadministered with fluvoxamine.

4 Q. And what conclusions did you draw from this?

5 A. That coadministration of tasimelteon and fluvoxamine  
6 greatly increases the exposure, both of the peak of the  
7 pulse, but also prolongs the dissipation, so that even at  
8 four hours after administration, you still have the amount  
9 of tasimelteon equivalent to the pulse that tasimelteon  
10 alone would have produced.

11 Q. When you say the "pulse," how is that depicted here  
12 in this figure?

13 A. It is -- starting with zero, is a rapid spike of the  
14 green line, and then the smooth and quick dissipation of  
15 this.

16 Q. Now, did Vanda also do work to study the effect of  
17 coadministration of rifampin with tasimelteon?

18 A. We did.

19 MR. GROOMBRIDGE: Let me ask you, Mr. Weir,  
20 please go to the next PDX, 3.3.

21 BY MR. GROOMBRIDGE:

22 Q. What is this we're looking at, Doctor?

23 A. Similar to the one before, green is tasimelteon alone  
24 concentration in the bloodstream, and tasimelteon plus  
25 rifampin in yellow.

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1 Q. And what conclusions did you draw from this?

2 A. That coadministration of tasimelteon and rifampin has  
3 a highly significant effect in reduction of tasimelteon,  
4 both the peak and the exposure.

5 Q. And in the context of treating Non-24, what would be  
6 the significance of that?

7 A. Most likely it will render tasimelteon ineffective  
8 because there will not be enough drug in the bloodstream.

9 Q. And, Doctor, did Vanda also do work to study the  
10 effect of ingesting food on the bioavailability of  
11 tasimelteon?

12 A. We did.

13 MR. GROOMBRIDGE: And, Mr. Weir, please put up  
14 PTX- 3.4.

15 BY MR. GROOMBRIDGE:

16 Q. What are we looking at here, Doctor?

17 A. Here we see the two conditions. Tasimelteon  
18 administered in a fasted situation versus the fed. And  
19 the fasted you see the rapid rise of the pulse and then  
20 the dissipation.

21 In the fed, however, the peak is lower and it shifted  
22 to the right. So that the areas under each curve appear  
23 to be about the same, but the height of the peak and the  
24 timing of the peak now have shifted down and to the right.

25 Q. What would be the significance of that in using

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1       tasimelteon to treat Non-24?

2       **A.**    It would be a dual concern.  One, you may not have  
3       enough of the pulse to be effective, and the shift to the  
4       right may shift into the, quote-unquote, phase delay part  
5       of the phase-response curve, actually having detrimental  
6       effects deregulating the circadian rhythm.

7       **Q.**    What's the delay part of the phase-response curve?

8       **A.**    It is a time that when you administer tasimelteon, it  
9       no longer shifts the time, or in the case of entrainment,  
10      maintain the given time but starts pushing the circadian  
11      rhythm to a later time.

12      **Q.**    Let me move on.

13                   **MR. GROOMBRIDGE:**  Please take that down,  
14      Mr. Weir.

15      **BY MR. GROOMBRIDGE:**

16      **Q.**    Dr. Polymeropoulos, could you turn to the next item  
17      in the binder, and hopefully you will find PTX- 185?

18      **A.**    Yes.

19      **Q.**    Do you recognize that?

20      **A.**    I do.

21      **Q.**    What is it?

22      **A.**    This is the study that looks at tasimelteon in  
23      combination with a CYP3A4 inhibitor, CYP3A4 inducer with  
24      time.

25                   **MR. GROOMBRIDGE:**  And, Your Honor, we offer

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1 Plaintiff's Exhibit 185 into evidence.

2 **MR. MILLIKEN:** No objection.

3 **THE COURT:** All right. It's admitted.

4 (PTX-185 is admitted into evidence.)

5 **BY MR. GROOMBRIDGE:**

6 **Q.** And, Doctor, does this document report the results of  
7 the work that Vanda did studying the effects of rifampin  
8 on tasimelteon?

9 **A.** It does.

10 **Q.** Now, let's move to the next item, please. Hopefully  
11 they will find JTX- 058.

12 Do you have that?

13 **A.** Yes.

14 **Q.** Do you recognize this?

15 **A.** Yes.

16 **Q.** What is it?

17 **A.** That is the study report of the food effect study on  
18 tasimelteon exposure.

19 **MR. GROOMBRIDGE:** We offer JTX- 58 into  
20 evidence.

21 **MR. MILLIKEN:** No objection.

22 **THE COURT:** It's admitted.

23 (JTX-58 is admitted into evidence.)

24 **BY MR. GROOMBRIDGE:**

25 **Q.** Doctor, does this report, JTX- 58, detail the results

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1 of the investigation that Vanda did into the effect of  
2 taking tasimelteon either with or without food?

3 **A.** Correct.

4 **Q.** I'd like to turn on to a different subject now.

5 Were you involved in the --

6 **THE COURT:** Before you do, just a procedural  
7 thing. So what's your plan on -- what's your intent as  
8 far as using these documents?

9 **MR. GROOMBRIDGE:** The -- what I want to do is  
10 make sure we have an evidentiary basis for -- they include  
11 the graphs that we just looked at, Your Honor.

12 **THE COURT:** Right. But I guess what I'm trying  
13 to figure out is how are they coming back?

14 So I follow Judge Robinson's rule that if it  
15 wasn't discussed, the documents drop from evidence. It's  
16 a bench trial, so, you know, I'm open to, if it's going to  
17 be used in some form, listening, but --

18 **MR. GROOMBRIDGE:** It already has --

19 **THE COURT:** What I'm not willing to tolerate is  
20 the Federal Circuit is different than the other circuits,  
21 in that you all get to try a case up there for the first  
22 time, and it's not right. And I'm not going to let that  
23 happen. And that's why Judge Robinson instituted the  
24 rule.

25 So how do we avoid that?

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1           **MR. GROOMBRIDGE:** Well, it already has been  
2       discussed, Your Honor, because there were three  
3       demonstratives, one from each of the last three documents.  
4       And I just did the demonstratives together because it  
5       saves a little bit of time from switching back and forth.

6           **THE COURT:** Okay.

7           **MR. GROOMBRIDGE:** And so the testimony is  
8       already in. I just wanted to make sure that we didn't  
9       just have a demonstrative, we actually had the underlying  
10      document from which the graph comes.

11          **THE COURT:** All right. So are there three  
12      different studies?

13          **MR. GROOMBRIDGE:** Yes.

14          **THE COURT:** Okay. And they all basically --  
15      you were trying to make the point that -- well, actually,  
16      what is the point you're trying to make? I mean, how this  
17      drug reacts with three other drugs?

18          **MR. GROOMBRIDGE:** Well, two drugs and with or  
19      without food.

20          **THE COURT:** Or with or without food, right.

21          **MR. GROOMBRIDGE:** And why it matters in the  
22      context of treating Non-24. In other words, the point is  
23      that it turns out you need that short sharp spike. And if  
24      you -- in these three circumstances, you compromise that.

25          **THE COURT:** Okay. All right.

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1           **MR. GROOMBRIDGE:** And I apologize. I just  
2       didn't --

3           **THE COURT:** Listen, I'm all for saving time,  
4       too. It is a balancing act. Saving time, which is good,  
5       especially on points that don't need to be unnecessarily  
6       repeated. The flip side is, you're slipping something  
7       into evidence that I'm not aware of. And then the first  
8       time I hear about it is when Law 360 covers the oral  
9       argument, and that happens. It's frustrating as a  
10      District Court judge when it happens. So that's what I'm  
11      trying to avoid.

12          **MR. GROOMBRIDGE:** I'd like to say, Your Honor,  
13      it won't happen in this case.

14          **THE COURT:** All right.

15          **MR. GROOMBRIDGE:** And I had forgotten that --  
16      Mr. Weir just reminded me that it actually takes a little  
17      bit of time to switch between different sources on the  
18      computer, which is why we find ourselves looking at the  
19      screens.

20          **THE COURT:** Okay. No problem.

21          **MR. GROOMBRIDGE:** Now --

22          **THE COURT:** Well, actually, maybe we should  
23      break for lunch. Can we come back at 1:00? Is a  
24      half-hour enough time for folks, or is it too tight?

25          **MR. GROOMBRIDGE:** It's okay with me,

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1 Your Honor.

2 **THE COURT:** Mr. Rozendaal, I think he wants to  
3 eat.

4 **MR. ROZENDAAL:** It's fine with us, Your Honor.

5 **THE COURT:** Hold on a second.

6 Well, I'll tell you what, why don't we come  
7 back at 1:15 and we will start. I have a discovery  
8 conference tomorrow at 8:30. It's the only time I can  
9 squeeze it in, so I have to do that. So it will be a  
10 little bit of a late start. So keep that in mind.

11 **MR. GROOMBRIDGE:** If it helps us not standing  
12 in the line outside, or stand there at a different time  
13 than everyone else.

14 **THE COURT:** We have three trials going in the  
15 building today. So it's just crazy. This is my ninth  
16 trial since October 25th.

17 **MR. ROZENDAAL:** But, Your Honor, before we  
18 break, you had asked a question earlier about the label  
19 and what does or doesn't need to be in it to show the  
20 intent.

21 **THE COURT:** Yes.

22 **MR. ROZENDAAL:** Mr. Groombridge pointed you to  
23 *AstraZeneca vs. Apotex*. I would, with the Court's  
24 permission, point you to *Gruntenthal GMBH vs. Alkem Labs*  
25 at 919 F.3d 1333, Federal Circuit 2019. I think is closer



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1 to our facts.

2 **THE COURT:** All right. Great. Thank you.

3 All right. So we will come back at 1:15. I  
4 will read it. You may step down. He is on direct. He is  
5 free to discuss with you all his testimony. Thank you.

6 (Recess was taken.)

7 **THE COURT:** All right. Mr. Groombridge.

8 **MR. GROOMBRIDGE:** Thank you, Your Honor.

9 **BY MR. GROOMBRIDGE:**

10 **Q.** Dr. Polymeropoulos, I'd like to switch to a different  
11 subject: Vanda's interactions with FDA.

12 Were you involved in that process?

13 **A.** Yes, I was.

14 **Q.** And was there a discussion with respect to  
15 entrainment between Vanda and the FDA?

16 **A.** Yes, there was.

17 **Q.** What was the substance of that discussion?

18 **A.** It was discussion in the context of the design of the  
19 clinical studies.

20 **Q.** Which clinical studies in particular?

21 **A.** The SET and RESET studies.

22 **Q.** And was there any disagreements between or difference  
23 of opinion between Vanda and the FDA on that subject?

24 **A.** Yes, there were.

25 **Q.** And what was it? Please explain.

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1     **A.**    Yes.  First of all, on the point of agreement was  
2     that the FDA and Vanda both agreed that the goal of  
3     treatment for Non-24 is to achieve entrainment; and by  
4     that, improve the relevant clinical outcomes.

5           The point of disagreement was Vanda preferred to  
6     declare, as the primary endpoint, the entrainment as seen  
7     by the position of the red stars, the acrophase, while the  
8     FDA preferred the clinical outcomes.

9     **Q.**    And how did that discussion progress?

10    **A.**    We agreed to disagree, and Vanda did both.  We  
11    introduced as a primary endpoint the point of acrophase  
12    and entrainment, and the endpoints as secondary end  
13    points.

14    **Q.**    And just to be clear, are we now talking about the  
15    clinical study or the label?

16    **A.**    The clinical study.

17    **Q.**    And --

18           **THE COURT:**  Can you stop for a second, please.  
19           What is the phrase that you've used, aqua  
20    phase?

21           **THE WITNESS:**  Acrophase.

22           **THE COURT:**  Acrophase?  A-C-R-O-P-H-A-S-E.

23           **THE WITNESS:**  Yes.

24           **THE COURT:**  Okay.

25           **THE WITNESS:**  It refers to the peak of

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1 melatonin, at the red stars.

2 **THE COURT:** Right. But it's two words, acro  
3 phase?

4 **THE WITNESS:** It is one word, A-C-R-O phase.

5 **THE COURT:** All right. Thank you.

6 **BY MR. GROOMBRIDGE:**

7 **Q.** And did there come a point when there was a meeting  
8 of the FDA advisory committee regarding tasimelteon?

9 **A.** Correct.

10 **Q.** And what is the role of an advisory committee in the  
11 drug approval process?

12 **A.** Advisory committee is a process during the review of  
13 a new drug application where the FDA asks, in a public  
14 forum, experts to review and opine on the improvability of  
15 a drug.

16 **Q.** And did you attend the advisory committee meeting for  
17 tasimelteon?

18 **A.** Yes, I did.

19 **Q.** And let me ask you to turn, please, in the binder to  
20 the next item, JTX-110.

21 As a preliminary question, are these the materials  
22 that were distributed by FDA in advance of that committee  
23 meeting to all the people who were going to be there?

24 **A.** That is correct.

25 **Q.** And did you receive a copy of them?

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1       **A.**     Yes.

2                   **MR. GROOMBRIDGE:**   Your Honor, we offer JTX-110  
3       into evidence.

4                   **MR. MILLIKEN:**   No objection.

5                   **THE COURT:**   It's admitted.

6                   (JTX-110 admitted into evidence.)

7                   **MR. GROOMBRIDGE:**   Mr. Weir, let's go to Page 3,  
8       please. And let's enlarge just the upper portion with the  
9       "to" and the "from," that information.

10                  **BY MR. GROOMBRIDGE:**

11       **Q.**     Dr. Polymeropoulos, this is a memo from someone  
12       called Ronald Farkas, MD, PhD.

13                  What was his role in this process?

14       **A.**     Dr. Farkas was the clinical team leader of the  
15       division.

16       **Q.**     And it says this is directed to members and invited  
17       guests of the committee.

18                  Were you one of the invited guests?

19       **A.**     Correct.

20       **Q.**     And what does it mean -- what's a "briefing memo" in  
21       this context?

22       **A.**     It is an introductory note to brief the position of  
23       the agency regarding the matters of the meeting.

24       **Q.**     And let's look down in this --

25                  **MR. GROOMBRIDGE:**   The last paragraph on Page 1,

1 let's enlarge that.

2 **BY MR. GROOMBRIDGE:**

3 **Q.** You see there, he says -- Dr. Farkas says:

4 Tasimelteon, a melatonin agonist, was studied in Non-24 to  
5 determine if it could, when taken at the same time before  
6 bed each night, provide a daily resetting of the circadian  
7 clock to take the place of an input from the eyes about  
8 light levels.

9 How does that relate to the idea of entrainment?

10 **A.** It is the definition of entrainment.

11 **MR. GROOMBRIDGE:** And if we go to the next  
12 page, let's, please, enlarge the second paragraph here.

13 **BY MR. GROOMBRIDGE:**

14 **Q.** Just so it's clear, what this is talking about,  
15 Dr. Jilapali, was that someone from FDA?

16 **A.** Yes, he was one of the interviewers.

17 **Q.** And Dr. Luan, is that also someone from FDA?

18 **A.** Correct.

19 **Q.** It says here that: During the development of  
20 tasimelteon, agreement was not reached between the sponsor  
21 and Division on the primary efficacy endpoint.

22 The sponsor, is that Vanda?

23 **A.** Correct.

24 **Q.** And division, is that FDA?

25 **A.** Yes.

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1     **Q.**   And is this talking about the discussion with regard  
2     to whether entrainment should be an endpoint in the study?

3     **A.**   Correct.

4     **Q.**   Why was it that Vanda wanted entrainment as measured  
5     by this metabolite of melatonin to be the endpoint in the  
6     study?

7     **A.**   For two reasons. That would be the scientifically  
8     required outcome to prove that a drug is effective in  
9     Non-24 Hour sleep-wake disorder; and the second was a  
10    cautious approach to make sure that we do not introduce  
11    confounders that could give a false negative answer.

12           In a small study, we wanted to use a more sensitive  
13    endpoint than the clinical endpoint, which would have been  
14    less sensitive.

15    **Q.**   When it says here: The Division -- meaning FDA --  
16    did not accept the biomarker-based endpoint, what is a  
17    biomarker-based endpoint in this context?

18    **A.**   A biomarker is actually extensively defined with the  
19    FDA regulations. It is an endpoint that does not directly  
20    measure how the patient feels, functions, or survives, but  
21    it is approximate.

22    **Q.**   What did you understand the FDA to be saying their  
23    position here when it states: A wealth of scientific --  
24    existing scientific knowledge about circadian rhythm  
25    suggested that the clinical benefit from entrainment in

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1 Non-24 would occur in a reasonably brief period of time  
2 and would be readily measurable in terms of benefit on  
3 sleep?

4 **A.** Yeah, that is a reflection of a regulatory position.  
5 That if you can measure the clinical outcome within a  
6 reasonable period of time, the FDA would prefer that you  
7 have that in addition to anything else for the disease; in  
8 this case, entrainment.

9 **Q.** And what does "clinical" -- and I see they've  
10 emphasized it here -- mean in this context?

11 **A.** Their definition is what I said earlier: The feel,  
12 function, or survive, something of direct clinical  
13 consequence.

14 **Q.** And did you have the discussion with the FDA  
15 following up on this in how it was that clinical benefit  
16 from entrainment might be shown and be readily measurable  
17 in terms of benefit on sleep?

18 **A.** Yes. We had quite a few discussions of that. And  
19 their concern was not whether entrainment is required to  
20 show a therapeutic effect on Non-24. It had to do with  
21 the clinical benefit which they agreed would derive from  
22 that entrainment.

23 **Q.** And did you --

24 **THE COURT:** I need to stop you. Sorry.

25 Can you repeat, please, what your definition of

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1 "clinical" is? You said --

2 **THE WITNESS:** Use the FDA's, how a patient will  
3 feel, function, or survive.

4 **THE COURT:** Okay. Thank you.

5 **BY MR. GROOMBRIDGE:**

6 **Q.** So just to maybe elucidate that a little. When FDA  
7 is talking about clinical benefit, they are saying how is  
8 this going to improve the perceptions of the patient who  
9 is being treated. Fair?

10 **A.** Correct.

11 **Q.** As opposed to a proxy or a surrogate that might be a  
12 measuring point that may or may not correlate to that  
13 improvement in condition for the patient; is that right?

14 **A.** Correct.

15 **Q.** I'd like to move on to the next paragraph, please.

16 **MR. GROOMBRIDGE:** Mr. Weir, could you put that  
17 up.

18 **BY MR. GROOMBRIDGE:**

19 **Q.** And did you have discussions with FDA about clinical  
20 endpoints that were identified here as lower quartile of  
21 nighttime sleep, total sleep, and nighttime total sleep  
22 time, and upper quartile of daytime total sleep duration?

23 **A.** We did.

24 **Q.** And how do these relate, if at all, to entrainment?

25 **A.** If we go up one to Non-24, in Non-24, as we saw in



1 the rest of the plots, even people who are not entrained,  
2 briefly they will come during the time where the sleep  
3 period is aligned with the circadian rhythm and they can  
4 sleep well.

5 In this case, we're trying to find if the drug works  
6 to correct a sleep disturbance when they are out of phase.  
7 So in order to do that, we elected the worst sleep  
8 represented by quartile, which would be a proxy of the out  
9 of circadian phase sleep.

10 **Q.** And "quartile" meaning 25 percent, correct?

11 **A.** Correct.

12 **Q.** And would it be fair to say that you discussed with  
13 FDA and decided that one of the things the study would  
14 look at would be the worst 25 percent of sleep that the  
15 subjects in the trial were having?

16 **A.** Correct.

17 **Q.** And why is that connected with entrainment?

18 **A.** It is connected with entrainment and associated with  
19 the quartile of daytime sleep. If you are entrained, you  
20 would expect improvement in the lower quartile of  
21 nighttime sleep; meaning, higher number of total sleep  
22 time and a decrease on the upper quartile of daytime total  
23 sleep duration decreasing. And this has to be in  
24 coincidence.

25 **Q.** And who proposed these endpoints regarding the

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1       quartiles?

2       **A.**     We did.

3       **Q.**     How did FDA respond?

4       **A.**     They accepted them.

5       **Q.**     Did they say anything when they accepted them with  
6       regard to entrainment?

7       **A.**     They understood that this is a derivation of  
8       entrainment. In fact, they asked us to do specific  
9       analysis to prove how they are related with the in-phase  
10      or the out-of-phase position of the circadian cycle.

11      **Q.**     And did you do that analysis?

12      **A.**     We did.

13      **Q.**     And did you submit it to FDA?

14      **A.**     And they reviewed it, yes.

15               **MR. GROOMBRIDGE:** Now, I'd like to look lastly  
16      at the label itself.

17               Your Honor, unless the Court wishes to study  
18      this further, we can take it down.

19               **THE COURT:** Fine.

20      **BY MR. GROOMBRIDGE:**

21      **Q.**     So would you turn, please, Dr. Polymeropoulos, to the  
22      next item in the binder, which should be JTX-28.

23      **A.**     Yes.

24      **Q.**     And is that the current approved label for Hetlioz;  
25      in other words, Vanda's tasimelteon product?

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1       **A.**     It is.

2       **Q.**     And does this label include the word "entrainment"?

3       **A.**     It does not.

4       **Q.**     Does it include the idea of entrainment?

5       **A.**     It includes the idea or the concept of entrainment.

6       **Q.**     Is there anything in the label that you would  
7 particularly point to with respect to how it includes the  
8 idea of entrainment?

9       **A.**     Yes. It is actually under the Clinical trial  
10 section.

11      **Q.**     Is that Page 12?

12      **A.**     Section 14.

13               **MR. GROOMBRIDGE:** Mr. Weir, let's put Page 12  
14 up on the screen, please.

15               **THE WITNESS:** Yes.

16               **MR. MILLIKEN:** Your Honor, I don't object to  
17 this exhibit. But I don't believe it's been actually  
18 offered into evidence.

19               **MR. GROOMBRIDGE:** Oh, I apologize. I forgot.  
20 Let me withdraw any pending question. And,  
21 Your Honor, we offer JTX-28.

22               **MR. MILLIKEN:** No objection.

23               **THE COURT:** All right. It's admitted.  
24 (JTX-28 admitted into evidence.)

25               **MR. GROOMBRIDGE:** Let's enlarge the first part

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1 of Section 14.

2 **BY MR. GROOMBRIDGE:**

3 **Q.** Dr. Polymeropoulos, is there something in this  
4 section of the label, Section 14.1, that you had in mind  
5 when you said it refers to the idea of entrainment?

6 **A.** There are several areas in the paragraph that starts  
7 with "study 2." In the last line, about the middle, where  
8 it starts with: Patients in whom the calculated time of  
9 peak melatonin level melatonin acrophase occurred at  
10 approximately the same time of day in contrast to the  
11 expected daily delay.

12 This is the definition of entrainment.

13 **Q.** And that melatonin acrophase, is that what was shown  
14 in the plot we looked at from the Lancet article by a red  
15 asterisk?

16 **A.** Yes.

17 **Q.** And so if those are occurring at approximately the  
18 same time each day, what does that tell you?

19 **A.** That the person is entrained.

20 **Q.** Does the label also include the upper and lower  
21 quartile information about which you just testified?

22 **A.** I believe it does.

23 **MR. GROOMBRIDGE:** Let me -- Mr. Weir, can you  
24 go to Page 13 and enlarge Table 3, please.  
25

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**BY MR. GROOMBRIDGE:**

**Q.** Dr. Polymeropoulos, what is this with respect as it may or may not relate to the quartile information?

**A.** It is actually the outcome of the two quartiles, the nighttime quartile and the daytime quartile. And it shows the results compared to the Hetlioz and placebo in study 1, the SET study, and study 2, the RESET study.

**Q.** It doesn't say "quartile." But does the use of 25 percent refer to quartile?

**A.** Correct.

**Q.** What does "most symptomatic" mean in this?

**A.** It means worst.

**Q.** And what was the result, as shown here, in terms of how the worst 25 percent of days were affected in terms of taking Hetlioz?

**A.** In regards to the nighttime worst quartile, it was increase of 50 minutes. And in regards to the daytime and napttime, there was a decrease of 49 minutes as compared to 22 increase and 22 decrease in minutes in the placebo respectively.

**Q.** Thank you.

**MR. GROOMBRIDGE:** And one last thing I'd like to cover while we have the label. Let's go, please, Mr. Weir to Page 5.

And let's enlarge Section 7.1 and 7.2 at the

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1 top.

2 **BY MR. GROOMBRIDGE:**

3 **Q.** Are these the drug-drug interaction parts of the  
4 label, Dr. Polymeropoulos?

5 **A.** They are.

6 **Q.** And you see that Section 7.2 refers to something  
7 called rifampin.

8 **A.** Correct.

9 **Q.** How is that related to rifampicin?

10 **A.** It is the same molecule.

11 **Q.** No one disagrees that those are synonyms; is that  
12 fair?

13 **A.** Correct.

14 **Q.** Does Vanda have any information with respect to  
15 whether Hetlioz or tasimelteon has been coadministered  
16 with rifampin?

17 **A.** Yes.

18 **Q.** What information?

19 **A.** We do not track this information, but we are aware of  
20 at least one case of coincident administration of the two.

21 **Q.** And similarly, with respect to the fluvoxamine, does  
22 Vanda have any information regarding coadministration of  
23 Hetlioz with fluvoxamine?

24 **A.** Not specific information. But certainly there are  
25 cases, given the comorbidity between the indication of

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1 fluvoxamine as indicated for obsessive-compulsive disorder  
2 where fluvoxamine is one of the first-line treatments.

3 **Q.** And what does "comorbidity" mean here?

4 **A.** Two disorders occurring in the same person at the  
5 same time. And in this case, I'm referring to Non-24 and,  
6 for example, a psychiatric condition like  
7 obsessive-compulsive disorder, yes.

8 **Q.** And as a practicing psychiatrist, did you, yourself,  
9 prescribe fluvoxamine?

10 **A.** I have.

11 **Q.** What is it used for?

12 **A.** It is used for obsessive-compulsive disorder and also  
13 it is approved for anxiety disorders.

14 **Q.** Thank you.

15 **MR. GROOMBRIDGE:** That concludes my questions.

16 **THE COURT:** Oh, you might have one more.

17 **MR. GROOMBRIDGE:** As usual, it's a helpful  
18 suggestion.

19 **BY MR. GROOMBRIDGE:**

20 **Q.** Dr. Polymeropoulos, why would obsessive-compulsive  
21 disorder and Non-24 be comorbid?

22 **A.** It is believed that for many psychiatric disorders,  
23 the underlying mechanism is deregulation of the circadian  
24 rhythm. And there is significant literature specifically  
25 on obsessive-compulsive disorder, that a big portion of

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1 cases will have circadian deregulation.

2 **MR. GROOMBRIDGE:** Thank you. That now  
3 concludes my questions.

4 **THE COURT:** All right.

5 **MR. MILLIKEN:** Your Honor, may we approach with  
6 some cross-examination binders?

7 **THE COURT:** Yes.

8 **MR. MILLIKEN:** May I proceed?

9 **CROSS-EXAMINATION**

10 **BY MR. MILLIKEN:**

11 **Q.** Good afternoon, Dr. Polymeropoulos. My name is Will  
12 Milliken. We met very briefly a couple of years ago at  
13 your deposition.

14 Nice to see you again.

15 **A.** Yes.

16 **Q.** Dr. Polymeropoulos, you are a Vanda stockholder,  
17 correct?

18 **A.** I am.

19 **Q.** You own about 4 percent of their shares; is that  
20 right?

21 **A.** Sounds right.

22 **Q.** All right. Let's talk about Non-24.

23 Typical complaints of Non-24 patients are sleep-wake  
24 complaints; is that right?

25 **A.** They are.



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1 Q. And fair to say that sleep-wake complaints sometimes  
2 prompt patients to seek treatment?

3 A. Correct.

4 Q. Okay. And if the symptoms that brought the patient  
5 in were to improve upon treatment, that would suggest that  
6 the treatment was at least in part effective, right?

7 A. Correct.

8 Q. Could you turn in your binder, please, to JTX-28.  
9 It's already into evidence. And this is the Hetlioz label  
10 that you were discussing with Mr. Groombridge.

11 A. Yes.

12 Q. Okay. And this label doesn't instruct the length of  
13 a patient's sleep period, right?

14 A. Could you please repeat?

15 Q. Sure.

16 The label doesn't instruct the length of the  
17 patient's sleep period, correct?

18 A. Correct.

19 Q. And it doesn't instruct people to sleep for a certain  
20 amount of time or duration, correct?

21 A. Correct.

22 Q. And the label also doesn't talk about what the target  
23 wake time should be, correct?

24 A. It does not.

25 Q. And it doesn't talk about what the target wake time

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1       should be relative to the target sleep time, correct?

2       **A.**    I think it talks about the nighttime episode, but  
3       there's no specific wake time, correct.

4       **Q.**    So you agree that it doesn't talk about what the  
5       target wake time should be relative to the target sleep  
6       time?

7       **A.**    Correct.

8       **Q.**    And I believe you said in your testimony with  
9       Mr. Groombridge, the label doesn't say the word  
10      "entrainment," correct?

11      **A.**    Correct.

12      **Q.**    All right. In your examination with Mr. Groombridge,  
13      I believe you stated that you cannot determine if a  
14      patient is entrained just by looking at their sleep.

15             Did I have that right?

16      **A.**    Just purely looking at the sleep duration, correct.

17      **Q.**    Okay. And so that would include their -- looking at  
18      their nighttime sleep duration and daytime sleep duration.  
19      Just by looking at that, you can't tell if they are  
20      entrained; is that fair?

21      **A.**    Correct.

22      **Q.**    And if you can turn in your binder to PTX-2, which is  
23      already in evidence. And I believe this is The Lancet  
24      article on which you are an author; is that right?

25      **A.**    I'm getting there. Is that in the front of the

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1 binder?

2 Q. I believe it should -- it's going to be in your  
3 second binder, I believe, PTX-2.

4 A. Yes.

5 Q. And if you could take a look at Page 7. And this is  
6 the 7 on the bottom middle of the document.

7 Oh, sorry. Go one page -- that's right. Yes. I  
8 think we have two different versions for some reason.

9 And you discussed this graph on the left side of the  
10 page with Mr. Groombridge; is that right?

11 THE COURT: Actually, can I -- Mr. Milliken,  
12 can we make sure we are using the same exhibit, because  
13 remember, I have to do this after trial. And if you all  
14 are referring to two different or three different exhibits  
15 but you are talking about the same chart, you can imagine  
16 how difficult that is for me and my clerk.

17 So if we can -- I don't know if this is from  
18 the same article, but, you know, and you are going to take  
19 too much to brief it and it's going to come back to me in  
20 June, and I'm going to have to start from scratch, and so  
21 it will be an absolute disaster.

22 MR. GROOMBRIDGE: I may be able to find the one  
23 so that we are all on the same page, if that's acceptable.

24 MR. MILLIKEN: It's on Page 8. I think we are  
25 all working off the same one now.

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1                   **THE COURT:** And what are we working off of?

2                   What's the exhibit number?

3                   **MR. MILLIKEN:** PTX-2.

4                   **THE COURT:** PTX-2? See, I don't think that was  
5                   what was used, was it?

6                   **MR. GROOMBRIDGE:** It is PTX-2, and it is the  
7                   2015 Lancet paper.

8                   **THE COURT:** I thought we were using PTX-816.

9                   **MR. MILLIKEN:** Your Honor, I believe that  
10                  that's a different paper in the same journal.

11                  **THE COURT:** Okay. Well, that explains it.  
12                  Okay.

13                  **MR. MILLIKEN:** Sorry for the confusion.

14                  **THE COURT:** And then hold up. Oh, and then we  
15                  were using PTX-2. Okay. Great.

16                  So now I'm on the same page you all are.

17                  Okay. Thank you very much.

18                  **MR. MILLIKEN:** Certainly.

19                  **BY MR. MILLIKEN:**

20                  **Q.** I believe you testified, Dr. Polymeropoulos, looking  
21                  at this --

22                  **A.** Sorry. Actually, I have Page 7.

23                  **Q.** I believe that we're all looking at the same -- is it  
24                  the graph that's displayed here on the screen?

25                  **A.** Yes, it is.

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1 Q. I believe you testified when you were speaking with  
2 Mr. Groombridge that you could tell this person entrained  
3 because the red asterisks were aligned at the same time  
4 each day; is that right?

5 A. Correct.

6 Q. And that red asterisk indicates the peak of the aMT6s  
7 melatonin metabolite; is that right?

8 A. Correct.

9 Q. And entrainment, as measured by that metabolite, that  
10 was a primary efficacy endpoint on the SET study; is that  
11 right?

12 A. Yes.

13 Q. All right. If you could go back to the label JTX-28,  
14 please. And if you could take a look at Table 3, which is  
15 in Section 14, the Clinical Studies section of the label.

16 A. Yes.

17 Q. And the efficacy endpoints shown there are nighttime  
18 sleep on 25 percent most symptomatic nights and  
19 daytime/naptime on 25 percent most symptomatic days,  
20 right?

21 A. Yes.

22 Q. And those are the only efficacy endpoints that are  
23 shown in Table 3; is that right?

24 A. Correct.

25 Q. And if you could now turn in your binder to DTX-139.

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1 And this is going to be toward the back of Volume 2.

2 **A.** Volume 2?

3 **Q.** Yes, sir.

4 **A.** I'm sorry, can you repeat the exhibit, DTX --

5 **Q.** DTX-139.

6 **A.** Yes.

7 **Q.** And this is a draft label for Hetlioz that Vanda  
8 proposed to the FDA; is that right?

9 **A.** It is a draft label. I'm not sure whether or not we  
10 proposed to the FDA.

11 **Q.** It is a Vanda-proposed label, though, you would  
12 agree?

13 **A.** It is a Vanda draft label. I'm not sure we proposed  
14 it.

15 **Q.** Okay. Fair enough.

16 **MR. MILLIKEN:** Your Honor, I move DTX-139 into  
17 evidence.

18 **MR. GROOMBRIDGE:** No objection.

19 **THE COURT:** All right. It's admitted.

20 (DTX-139 admitted into evidence.)

21 **BY MR. MILLIKEN:**

22 **Q.** If could you take a look, please, at the second  
23 paragraph under the Dosage and Administration section on  
24 the first page of that label.

25 **A.** Yes.

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1 Q. And specifically the first sentence.

2 So this Vanda draft label did say the word  
3 "entrainment," right?

4 A. Correct.

5 Q. But the FDA didn't accept that specific language for  
6 inclusion in the approved Hetlioz label, right?

7 A. That specific language does not appear on the Hetlioz  
8 label.

9 Q. That language was proposed to the FDA, correct?

10 A. I don't know if it was.

11 Q. Dr. Polymeropoulos, you testified in a deposition in  
12 this case, correct?

13 A. I testified in deposition?

14 Q. Earlier in this case you testified --

15 A. Yes.

16 Q. -- in a deposition.

17 Were you under oath during that deposition?

18 A. Yes.

19 Q. You swore to tell the truth?

20 A. I did.

21 Q. And you did tell the truth, didn't you?

22 A. Yes.

23 Q. And your lawyer was with you, correct?

24 A. Yes.

25 Q. You had an opportunity to review the transcript for

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1 any errors?

2 **A.** Yes.

3 **Q.** Could you take a look, please, at the beginning of  
4 Volume 1 of your binder. There should be a tab that  
5 refers to a 12/20/19 deposition transcript.

6 **A.** What is the exhibit?

7 **Q.** The tab says -- it's in the very front of Volume 1.  
8 And the tab says: Polymeropoulos 12/20/2019.

9 **A.** That's in Volume 1?

10 **Q.** It is in Volume 1. Yes, sir.

11 **A.** Yes.

12 **Q.** And if could you turn, please, to Page 112 of that --  
13 or sorry. Before you do that, could you look at the cover  
14 and confirm that this is a transcript of a deposition that  
15 you gave on Friday, December 20th, 2019 in this case?

16 **A.** Correct.

17 **Q.** Okay. And if you could turn, please, to Page 112.

18 **A.** Yes.

19 **Q.** And specifically, I'm beginning at Line 14:

20 "Q. Okay. And did the FDA accept this label?

21 "A. That specific language? Are you pointing to the  
22 paragraph, entrainment, the big paragraph in dosage  
23 administration?

24 "Q. Yeah.

25 "A. That does not appear in the dosage and administration



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1 of the 2014 label, but I believe the final label as well,  
2 the current one.

3 "Q. Did Vanda kind of just voluntarily abandon that  
4 language or did FDA essentially say, you can't have that  
5 in there, or something else?

6 "A. We proposed that to the FDA.

7 "Q. Okay.

8 "A. The FDA did not accept that language."

9 Was that your testimony?

10 A. Yes.

11 Q. And then in that draft Vanda label, if you could go  
12 to Page 12, it says DTX-139, 12 on the bottom of it.

13 A. Yes. Back to the other binder?

14 Q. Right. Back to DTX-139, which is in the second  
15 binder. Sorry to make you jump around.

16 A. Yes.

17 Q. If you take a look at Table 2 there, Table 2 does  
18 include the data regarding aMT6s acrophase endpoint,  
19 correct?

20 A. Table 2, yes.

21 Q. Thank you.

22 Can you put that document aside for now.

23 If you could turn -- this is also in Volume 2 -- to  
24 JTX-115.

25 A. Yes.

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1 Q. And this is a Vanda document that says Promotional  
2 Messaging Guidebook on the front; is that right?

3 A. Correct.

4 Q. And it's dated August 2014; is that right?

5 A. Correct.

6 MR. MILLIKEN: Your Honor, I move JTX-115 into  
7 evidence.

8 MR. GROOMBRIDGE: No objection.

9 THE COURT: All right. It's admitted.

10 (JTX-115 admitted into evidence.)

11 BY MR. MILLIKEN:

12 Q. This is a document that was used in training sales  
13 representatives a few months into the launch of Hetlioz;  
14 is that right?

15 A. Yes.

16 Q. And this is part of the training for when sales  
17 representatives are talking to physicians, things they  
18 should do and should not do, right?

19 A. Correct.

20 Q. And if you take a look at the second slide, second  
21 page of the document, it says: Message review, staying on  
22 label. Right?

23 A. Yes.

24 Q. And then on the third slide, at the top it says, in  
25 all capital letters: Entrainment should not be used to

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1 convey efficacy of Hetlioz. Right?

2 **A.** Yes.

3 **Q.** And then down there at the bottom, entrained and  
4 entrainment are listed under terms to avoid, right?

5 **A.** Correct.

6 **Q.** And, in fact, talking about entrainment on the part  
7 of the sales representatives would run afoul of Vanda's  
8 negotiation the FDA regarding the label, right?

9 **A.** Where does it say that?

10 **Q.** No. Not with regard to the document, I'm just asking  
11 you, talking about entrainment by the sales  
12 representatives would run afoul of Vanda's negotiation  
13 with the FDA regarding the label, right?

14 **A.** I would say that Vanda would not want to use a word  
15 that is not on the label.

16 **Q.** Okay. So Vanda told the sales representatives not to  
17 say "entrainment" because that word wasn't on the label;  
18 is that fair?

19 **A.** The word was not on the label, correct.

20 **Q.** Okay. If you can now turn to JTX-99, which is also  
21 in Volume 2. Should be the same binder.

22 **A.** Yes.

23 **Q.** And this is a Vanda document that's titled: Hetlioz  
24 Solutions and Case Management Field use. Right?

25 **A.** Correct.

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1     **Q.**   And these are directions for sales representatives,  
2     right?

3     **A.**   Yes.

4                 **MR. MILLIKEN:**   Your Honor, I move JTX-99 into  
5     evidence.

6                 **MR. GROOMBRIDGE:**   No objection.

7                 **THE COURT:**   That's admitted.

8                         (JTX-99 admitted into evidence.)

9     **BY MR. MILLIKEN:**

10    **Q.**   Take a look at Page 2, please.   The sales team was  
11    instructed not to say that Non-24 hour disorder was  
12    characterized by lack of entrainment, right?

13    **A.**   It is in the Terms to Avoid column, lack of  
14    entrainment.

15    **Q.**   Okay.   And also in the terms to avoid, the sales team  
16    was not -- was instructed not to state that the Hetlioz  
17    shifted the master body clock, right?

18    **A.**   I'm sorry?

19                 Correct.

20    **Q.**   And then on Page 4, you take a look at the Terms to  
21    Avoid column, about five cells down, entrain and  
22    entrainment are listed as terms to avoid, right?

23    **A.**   Correct.

24    **Q.**   And the sales team was instructed not to say these  
25    things because Vanda didn't want the sales force to use

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1 any term or words that are not in the label, correct?

2 **A.** Any what words?

3 **Q.** Vanda didn't want the sales force to use any term or  
4 words that were not in the label.

5 **A.** Correct.

6 **Q.** Let's switch gears for a moment.

7 As of 2004, you'd agree there was extensive  
8 literature demonstrating the ability of melatonin to phase  
9 advance circadian rhythms.

10 **A.** There was literature that suggested that melatonin  
11 can advance circadian rhythms.

12 **Q.** And, in fact, there was extensive literature  
13 demonstrating the melatonin could phase advanced circadian  
14 rhythms, right?

15 **A.** I don't know how you define "extensive." There were  
16 a few publications.

17 **Q.** So under your understanding of the word "extensive,"  
18 would you agree with me that as of 2004, there was  
19 extensive literature demonstrating the ability of  
20 melatonin to phase advance circadian rhythms?

21 **A.** The extensive -- the reason I hesitate for  
22 "extensive" is the field of circadian research and biology  
23 is small. There are few researchers conducting it.  
24 There's not a tremendous amount of literature.

25 Whether there were good publications to that matter,

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1 I would agree.

2 Q. But your issue is with the word "extensive." You  
3 wouldn't agree that the literature demonstrating the  
4 ability of melatonin to phase advance circadian rhythms  
5 was extensive.

6 A. I don't know how to measure extensive.

7 Q. And as of 2004, there's literature showing that in  
8 some circumstances, melatonin could shift circadian  
9 rhythms, right?

10 A. Correct.

11 Q. Could you turn, please -- and this is actually going  
12 to be in your direct binder that Mr. Groombridge gave you,  
13 the white one -- to PTX-816.

14 A. Yes.

15 Q. And this is an article from 2009 on which you are  
16 listed as an author, right?

17 A. Correct.

18 Q. And it's about tasimelteon?

19 A. Correct.

20 Q. Could you take a look at Page 9 of this document.  
21 It's -- and I'd like you to look at the second full  
22 paragraph on the right-hand column.

23 A. I'm sorry. This is on Page 9?

24 Q. PTX-816, Page 9, I believe.

25 A. Okay. I was in the next document. I'm sorry.

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1 Yes.

2 Q. And do you see the second full paragraph on the  
3 right-hand column?

4 A. That starts with?

5 Q. With "We suggest"?

6 A. Yes, I see that.

7 Q. And so you concluded, in February 2009, that a  
8 phase-shifting drug, such as tasimelteon, has therapeutic  
9 potential for circadian rhythm sleep disorders, correct?

10 A. That is what the sentence says, yes.

11 Q. You can put that aside.

12 Vanda's required to file Form 10-Ks with the SEC,  
13 correct?

14 A. Correct.

15 Q. And those 10-K filings are publicly available.

16 A. They are.

17 Q. And you review every Vanda 10-K before it's  
18 submitted, correct?

19 A. I do.

20 Q. If you could turn, please, to PTX-473 now back in  
21 your black binder, and specifically Volume 2.

22 A. Would you please repeat that, the tab number?

23 Q. It is PTX-473.

24 A. Yes.

25 Q. This is Vanda's 10-K for the fiscal year ended

**Polymeropoulos - Cross**

1 December 31, 2010; is that right?

2 **A.** Correct.

3 **MR. MILLIKEN:** Your Honor, I move PTX-473 into  
4 evidence.

5 **MR. GROOMBRIDGE:** No objection.

6 **THE COURT:** It's admitted.

7 (PTX-473 admitted into evidence.)

8 **BY MR. MILLIKEN:**

9 **Q.** If you could turn, please, to the -- near the back of  
10 the document, Page 109.

11 **A.** Yes.

12 **Q.** That's your name there; is it not?

13 **A.** It is.

14 **Q.** And you stated here that you've reviewed this 10-K?

15 **A.** Yes.

16 **Q.** And you state that to the best of your knowledge,  
17 this report didn't contain any untrue or misleading  
18 statements; is that right?

19 **A.** Correct.

20 **Q.** And you signed this and dated it on March 10, 2011;  
21 is that right?

22 **A.** Correct.

23 **Q.** And this document was available to the public before  
24 2012, right?

25 **A.** Yes.



***Polymeropoulos - Cross***

1 Q. If could you turn back to Page 5 of the document.

2 A. Yes.

3 Q. And then you see the second bullet point on that page  
4 that begins "Tasimelteon"?

5 A. I do.

6 Q. And it states here that: Tasimelteon is a compound  
7 for the treatment of sleep and mood disorders, including  
8 circadian rhythm sleep disorders?

9 A. Correct.

10 Q. And it goes on to say that: The compound binds  
11 selectively to the brain's melatonin receptors, which are  
12 thought to govern the body's natural sleep-wake cycle?

13 A. Correct.

14 Q. And then it goes on to say that: Compounds that bind  
15 selectively to these receptors are thought to be able to  
16 help treat sleep disorders?

17 A. Correct.

18 Q. And the following sentence states that: Vanda  
19 announced positive results from its trials in transient  
20 insomnia and chronic primary insomnia.

21 Is that right?

22 A. The first sentence only refers to the Phase III  
23 transient insomnia November 2006.

24 Q. And then the following sentence states that:  
25 Positive topline results in the study of chronic primary

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1 insomnia were also announced?

2 **A.** Yes.

3 **Q.** If you could flip to the next page, Page 6. And it  
4 says there at the top that: Vanda initiated two clinical  
5 trials to pursue FDA approval of tasimelteon for the  
6 treatment of Non-24 Hour sleep-wake disorder in blind  
7 individuals without light perception in the third quarter  
8 of 2010?

9 **A.** Correct.

10 **Q.** A couple sentences later, it also states that: Those  
11 trials were going to include laboratory measures of the  
12 synchronization between the internal body clock and the  
13 24-hour environmental light/dark cycle?

14 **A.** Is that what you just highlighted, the trial has a  
15 six-month treatment period?

16 **Q.** Correct, the sentence beginning there. It states:  
17 The trial has a six-month treatment period and includes  
18 measures of both nighttime and daytime sleep, as well as  
19 laboratory measures of the synchronization between the  
20 internal body clock and the 24-hour environmental  
21 light/dark cycle.

22 **A.** I see that, yep.

23 **Q.** Okay. And then on the next page, the first full  
24 sentence on the very top, it states that: Tasimelteon may  
25 represent a breakthrough based on the compound's

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1 demonstrated efficacy and safety to date and its novel  
2 mechanism of action.

3 Do you see that?

4 **A.** I do.

5 **Q.** And given that you certified to the accuracy of this  
6 statement -- or the accuracy of the statements in this  
7 document, I assume you would agree that was true as of  
8 March 2011?

9 **A.** Correct.

10 **Q.** And then if you could turn, please, to Page 11. Do  
11 you see a heading that says: Potential Advantages of  
12 Tasimelteon?

13 **A.** I do.

14 **Q.** And the second-to-last sentence in that paragraph  
15 says that: For patients with CRSDs, tasimelteon may be  
16 able to align the patient's sleep-wake cycle with his or  
17 her lifestyle.

18 Do you see that?

19 **A.** Correct.

20 **Q.** And that's talking about entrainment, right?

21 **A.** Not necessarily. Alignment can also happen in  
22 delayed sleep phase disorder or jetlag or shift worker  
23 shift disorder.

24 **Q.** So it's your testimony that when the document says  
25 that "tasimelteon may be aligned" -- may be able to align

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1 a patient's sleep-wake cycle with his or her lifestyle,"  
2 that's not necessarily referring to entrainment?

3 **A.** It depends on the context of the indication.

4 **Q.** Okay. And then as support for that statement that we  
5 were just looking at, and the final sentence of that  
6 paragraph, the document cites Vanda's Phase II trial of  
7 tasimelteon in transient insomnia, right?

8 **A.** Correct.

9 **Q.** All right. Let's switch gears again.

10 Could you go in your binder -- and I think this  
11 should be in Volume 1 -- JTX-1?

12 **A.** Yes.

13 **Q.** And this is a patent on which you're listed as an  
14 inventor; is that right?

15 **A.** Correct.

16 **Q.** It is one of the patents asserted in this case,  
17 right?

18 **A.** Yes.

19 **MR. MILLIKEN:** Your Honor, I'd move JTX-1 into  
20 evidence.

21 **MR. GROOMBRIDGE:** No objection.

22 **THE COURT:** It's admitted.

23 (JTX-1 admitted into evidence.)

24 **BY MR. MILLIKEN:**

25 **Q.** Can we take a look at Claim 1? And that's on

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Page 42.

**A.** Page 42. You mean Page 41?

**Q.** I apologize. It is Page 41.

And do you see there that Claim 1 requires, among other things, a daily sleep period of approximately seven-to-nine hours?

**A.** It says a daily sleep period of approximately seven-to-nine hours. I don't see the "requiring."

**Q.** Sorry. I will rephrase the question.

The claim contains the phrase, "a daily sleep period of approximately seven-to-nine hours." Right?

**A.** Correct.

**Q.** And it's your position that someone who allocates five hours to sleep is allocating approximately seven-to-nine hours of sleep, right?

**A.** Five hours, maybe, is -- is a sleep period which is outside of the seven-to-nine hours.

**Q.** But it's your position that five hours is approximately seven-to-nine hours, right?

**A.** It could be, depending how you define "approximately." The intent of this is to suggest a sleep opportunity period of seven-to-nine hours which would be recommended for most people.

**Q.** So my question is, under your understanding of this phrase, if a patient has a daily sleep period of five

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1 hours, you would say that that patient had a daily sleep  
2 period of approximately seven-to-nine hours; is that fair?

3 **A.** I don't understand how you connect the five hours to  
4 this phrase.

5 **Q.** So the claim says, "a daily sleep period of  
6 approximately seven to eight hours." And if I allocate  
7 five hours of sleep, it's your position that I have  
8 allocated approximately seven-to-nine hours to sleep; is  
9 that fair?

10 **A.** I would -- I don't think that I should be construing  
11 the claim, but I would say the five hours seems to be a  
12 little too far away from the seven to nine.

13 **Q.** Okay. So five hours is not approximately  
14 seven-to-nine hours?

15 **A.** Correct.

16 **Q.** Could you go back to the very front tab in Volume 1,  
17 your December 20, 2019 deposition?

18 **A.** Yes.

19 **Q.** The tab says Polymeropoulos, and it has the date,  
20 which is December 20th, 2019.

21 **A.** Correct.

22 **Q.** And if you could turn, please, to Page 184.

23 **A.** Yes.

24 **Q.** And I'm starting at Page 184, Line 19:

25 **"Q.** Okay. So that person who allocates five hours of

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1 sleep, five hours to sleep, is that someone who allocates  
2 approximately seven-to-nine hours?

3 **"A.** Yes."

4 Was that your testimony?

5 **A.** I'm sorry, can you point me again?

6 **Q.** Page 184, beginning at Line 19.

7 **A.** Nineteen.

8 **Q.** It says:

9 **"Q.** Okay. So that person who allocates five hours of  
10 sleep, five hours to sleep, is that someone who allocates  
11 approximately seven-to-nine hours?

12 **"A.** Yes."

13 Was that your testimony?

14 **A.** That was my testimony.

15 **Q.** All right. Some forms of insomnia are classified as  
16 circadian rhythm sleep disorders; is that fair?

17 **A.** Some form of insomnia?

18 **Q.** Some forms of insomnia are classified as circadian  
19 rhythm sleep disorders.

20 **A.** I believe that circadian rhythm disorders are their  
21 own category in the International Classification of  
22 Disease. Insomnia is a symptom within CRSD.

23 **Q.** So you don't agree that some forms of insomnia are  
24 actually classified as circadian rhythm sleep disorders?

25 **A.** I'm not sure I recall exactly how the Classification

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1 of Disease classifies them.

2 **Q.** Okay. That's fair.

3 Could you turn -- and this should be the very next  
4 tab in your binder. It's another deposition transcript.

5 And could you confirm that this was the transcript  
6 from your November 18th, 2020 deposition?

7 **A.** What exhibit?

8 **Q.** It's the tab following the transcript that we were  
9 just looking at.

10 **A.** Yes.

11 **Q.** And you were also under oath during this deposition,  
12 correct?

13 **A.** Correct.

14 **Q.** And you told the truth.

15 **A.** Yes.

16 **Q.** If you could go, please, to Page 66 of that  
17 transcript.

18 **A.** Yes.

19 **Q.** Beginning at Line 55 -- or excuse me, Page 66,  
20 Line 7:

21 **"Q.** Is insomnia classified as a circadian rhythm sleep  
22 disorder?

23 **"A.** Some forms of insomnia are classified as circadian  
24 rhythm sleep disorders, and insomnia can be a symptom."

25 Was that your testimony?



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1     **A.**     Correct.

2     **Q.**     Now, in response to some of Mr. Groombridge's  
3     questioning, you said that Vanda did some drug-drug  
4     interaction studies concerning tasimelteon; is that right?

5     **A.**     Yes.

6     **Q.**     And when you did drug-drug interaction studies on  
7     tasimelteon, you had information suggesting that  
8     tasimelteon was metabolized by CYP1A2, correct?

9     **A.**     It was some preliminary information from BMS,  
10    correct.

11    **Q.**     And that was one of the factors that resulted in  
12    Vanda testing a CYP1A2 inhibitor with tasimelteon, right?

13    **A.**     One of the factors, correct.

14    **Q.**     And Vanda also did a study about the coadministration  
15    and tasimelteon with CYP3A4 inducers, right?

16    **A.**     Correct.

17    **Q.**     And you did that, in part, based on knowledge that  
18    CYP3A4 may be contributing to the metabolism of  
19    tasimelteon, right?

20    **A.**     My recollection is that BMS thought that it may not.

21    **Q.**     Yes. But my question is at the time that Vanda  
22    performed its drug-drug interaction studies involving  
23    CYP3A4 inducers, you did that, in part, based on knowledge  
24    that CYP3A4 may be contributing to the metabolism of  
25    tasimelteon; is that fair?

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1       **A.**    It is possible, yes.

2       **Q.**    Okay. Do you recall -- or actually, if you would, if  
3       you could turn to PTX-613.

4       **A.**    Is that the other book?

5       **Q.**    That's going to be in Volume 2 of the binder.

6       **A.**    Yes.

7       **Q.**    And this is one of the documents that you looked at  
8       with Mr. Groombridge; is that right?

9       **A.**    Correct.

10      **Q.**    This was a confidential document, wasn't it?

11      **A.**    Correct.

12      **Q.**    It wasn't available to the public.

13      **A.**    Correct.

14      **Q.**    And then if you could turn now to JTX- 111, which I  
15      believe should be in the same binder.

16      **A.**    Yes.

17      **Q.**    This was also a confidential document?

18      **A.**    Correct.

19      **Q.**    And it wasn't available to the public either?

20      **A.**    It was not.

21      **Q.**    All right. You talked some with Mr. Groombridge  
22      about the two drug-drug interaction studies and the food  
23      effect study that Vanda did with tasimelteon.

24             Do you recall that?

25      **A.**    Correct.

**Polymeropoulos - Cross**

1 Q. Each of those studies was in healthy volunteers,  
2 correct?

3 A. It was.

4 Q. Turning now to the SET and RESET studies. Those  
5 studies were conducted administering the drug before  
6 bedtime, right?

7 A. Correct.

8 Q. And administration was several hours after a meal?

9 A. I don't think there was a specification about the  
10 timing after a meal in protocol.

11 Q. So you don't recall whether the administration was  
12 several hours after the meal in the SET and RESET studies?

13 A. I do not. I don't think it was specified.

14 Q. Could you turn back in Volume 1 of your binder to --  
15 it's going to be the second tab. This is the November 18,  
16 2020 deposition transcript.

17 A. Okay.

18 Q. If you could turn to Page 72, please.

19 A. Okay.

20 Q. Beginning at Page 72, Line 25.

21 A. I'm sorry.

22 Page 72, yes.

23 Q. Okay.

24 "Q. The SET and RESET studies did not study the effect of  
25 the food effect on Tmax, correct?"

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1     **A.**    I'm sorry. I must be on the wrong page. I am  
2     looking at Page 70 to 73.

3     **Q.**    Are you in the correct transcript? This is the  
4     11/18/2020 transcript.

5     **A.**    Okay. Seventy-two, yes.

6     **Q.**    And you were asked:

7         **"Q.** The SET and RESET studies did not study the effect of  
8         the food effect on Tmax?"

9     **A.**    I'm sorry, I don't see that. This starts:

10         "Before I answer, sir, okay, would you mind  
11         repeating?"

12         That's 72.

13     **Q.**    Let me make sure we're -- all right. You are looking  
14     at the transcript that has November 18th, 2020 at the top?

15     **A.**    Correct.

16     **Q.**    And you are looking at Page 72?

17     **A.**    Correct.

18     **Q.**    And Line 25 of Page 72?

19     **A.**    Yes. The SET and RESET studies.

20     **Q.**    Yes.

21     **A.**    Yes, I see that.

22     **Q.**    Okay. And you were asked the question:

23         **"Q.** The SET and RESET studies did not study the effect of  
24         the food effect on Tmax, correct?

25         **"A.** They were conducted administering the drug before

**Polymeropoulos - Cross**

1       bedtime and several hours after the meal. So there were  
2       in the SET and RESET studies Hetlioz was not administered  
3       with food."

4       Was that your testimony?

5       **A.**    It was.

6       **Q.**    And SET and RESET didn't study the effect of food on  
7       the administration of tasimelteon, correct?

8       **A.**    Correct.

9       **Q.**    You talked with Mr. Groombridge a bit about BMS.

10       BMS never tried to develop tasimelteon for the  
11       treatment of Non-24, right?

12       **A.**    It did not.

13       **Q.**    And Vanda is not aware of any clinical data that  
14       compare melatonin and tasimelteon in head-to-head trials;  
15       is that right?

16       **A.**    We have not done such a study, correct.

17       **Q.**    Could you turn, please -- and this will still be in  
18       Volume 1 -- to JTX-12.

19       **A.**    Yes.

20       **Q.**    And this is US patent 5,856,529, right?

21       **A.**    Correct.

22               **MR. MILLIKEN:** Your Honor, I move JTX-12 into  
23       evidence.

24               **MR. GROOMBRIDGE:** No objection.

25               **THE COURT:** All right. It's admitted.

**Polymeropoulos - Cross**

(JTX-12 admitted into evidence.)

**BY MR. MILLIKEN:**

**Q.** BMS granted an exclusive license to this '529 patent to Vanda in 2004; is that correct?

**A.** Correct.

**Q.** And if you could look, please, at JTX-103, which is in Volume 2 of your binder.

**A.** Yes.

**Q.** And this is the license agreement between BMS and Vanda that included the '529 patent, right?

**A.** Correct.

**MR. MILLIKEN:** Your Honor, I move JTX-103 into evidence.

**MR. GROOMBRIDGE:** No objection.

**THE COURT:** All right. It's admitted.

(JTX-103 admitted into evidence.)

**BY MR. MILLIKEN:**

**Q.** Okay. Let's go back to the '529 patent, JTX-12.

**A.** Okay.

**Q.** This patent covers tasimelteon, right?

**A.** Correct.

**Q.** And this patent is still in force.

**A.** It is.

**Q.** It hasn't expired.

**A.** Correct.

**Polymeropoulos - Cross**

1     **Q.**    So if someone else besides Vanda were to sell  
2     tasimelteon in the United States, that would infringe the  
3     patent, right?

4     **A.**    I have to ask my lawyers how this works, but I  
5     believe it to be so.

6     **Q.**    That's fair enough.

7           And if we take a look at Page 24 of the '529 patent,  
8     it should have Claim 14 on it. The '529 patent also  
9     covers the use of tasimelteon to treat circadian rhythm  
10    disorders, right?

11    **A.**    Correct.

12    **Q.**    Okay. And could you now turn -- sorry to make you go  
13    back to Volume 2, but if you could turn to PTX-633.

14    **A.**    Is it in the other book?

15    **Q.**    It's in the other book, yes, sir.

16    **A.**    PTX?

17    **Q.**    PTX-633.

18    **A.**    Yes.

19    **Q.**    And this is the patent and exclusivity information in  
20    the Orange Book listing for Hetlioz, right?

21    **A.**    Correct.

22           **MR. MILLIKEN:** And, Your Honor, I move PTX-633  
23    into evidence.

24           **MR. GROOMBRIDGE:** No objection.

25           **THE COURT:** It's admitted.

**Polymeropoulos - Redirect**

(PTX-633 admitted into evidence.)

**BY MR. MILLIKEN:**

**Q.** The '529 patent is listed here on this document, correct?

**A.** Correct.

**Q.** See there where it says "patent use code" and then next to the '529 patent, it says "U2149"?

**A.** I see that.

**Q.** Do you know what U2149 means?

**A.** I'm not sure.

**Q.** Would it surprise you to know that use code U2149 is treatment of Non-24 Hour sleep-wake Disorder by administering tasimelteon?

**A.** No.

**MR. MILLIKEN:** No further questions.

**THE COURT:** All right. Any redirect?

**MR. GROOMBRIDGE:** A little, Your Honor. Yes.

**REDIRECT EXAMINATION**

**BY MR. GROOMBRIDGE:**

**Q.** Dr. Polymeropoulos, do you have the black binder with the deposition transcripts in it in front of you there?

**A.** Is that Volume 2 or 1?

**Q.** It is Volume 1, I believe.

**A.** Yes.

**Q.** And Mr. Milliken asked you about some testimony from



**Polymeropoulos - Redirect**

1 your November 18th, 2020 deposition, beginning at the end  
2 of Page 72 and carrying on to Page 73.

3 Can you find those pages, please?

4 **A.** Yes.

5 **Q.** And immediately after the question and answer that  
6 was pointed to, did you give the following testimony:

7 "Q. And there were not studies to study the effect of  
8 food on the administration of tasimelteon, correct?

9 "A. You mean studies -- you still mean SET and RESET?

10 "Q. Yes.

11 "A. Yeah. Those studies did not take patients with and  
12 without food."

13 Was that your testimony at the deposition?

14 **A.** Correct.

15 **Q.** Now, I would like to talk a little bit about daily  
16 sleep period, or maybe just ask one question.

17 As you understand the term, does daily sleep period  
18 refer to how long someone sleeps for; in other words,  
19 sleep duration?

20 **A.** Sleep period --

21 **Q.** Correct.

22 **A.** -- is the allotted time for a sleep opportunity.

23 **Q.** And how does that relate to sleep duration?

24 **A.** Duration is the amount of sleep that one slept in the  
25 period, be it day or nighttime.

*Polymopoulos*

1 Q. Does a sleep period of approximately seven-to-nine  
2 hours connote how much time the person actually sleeps?

3 A. No.

4 Q. One final thing. I'd like to look at the sales  
5 documents that Mr. Milliken showed you.

6 Let's start -- can you find JTX-115, which is in  
7 Volume 2 of the black binders.

8 MR. GROOMBRIDGE: And Mr. Weir, could you put  
9 that up and find Page 3, please.

10 Let's enlarge it, please.

11 BY MR. GROOMBRIDGE:

12 Q. Now, Mr. Milliken showed you this and said -- asked  
13 you whether the sales force was allowed to use the word  
14 "entrainment."

15 Do you recall?

16 A. Yes.

17 Q. Dropping down where it says Preferred Terms here,  
18 what are the terms that the sales force is allowed to use?

19 A. The term "aligns sleep-wake cycle to the 24-hour day"  
20 is a primary preference, and the second option,  
21 "synchronizes sleep-wake cycles to the 24-hour day."

22 Q. And how do those relate, if at all, to entrainment?

23 A. They're synonymous.

24 MR. GROOMBRIDGE: Thank you. No more  
25 questions.

*Polymenopoulos*

1           **THE COURT:** All right. Well, this is a bench  
2 trial. I have a few questions for you, Doctor.

3           So this test -- let's look at PTX-2, right,  
4 this test summarized here.

5           **THE WITNESS:** The PTX is right here, yes.

6           **THE COURT:** All right. Actually, so this has  
7 these asterisks, right? And as I understand it, you are  
8 saying they measure the peak aMT6s melatonin metabolite;  
9 is that right?

10          **THE WITNESS:** Metabolite of melatonin.

11          **THE COURT:** I wrote down as the peak AMT6s  
12 melatonin metabolite -- or metabolite, I should say.

13          **THE WITNESS:** That is correct.

14          **THE COURT:** That's right. Okay. That's what  
15 it measures here.

16          So what do you give -- now, how do you measure  
17 this? Do you give people a bottle to take a urine test at  
18 a certain time every day? What is it that you do to come  
19 up with that measurement?

20          **THE WITNESS:** The way it was measured is,  
21 people collected the entire 24 hour, as they had different  
22 episodes. They marked the times that the jars were  
23 filled. And we sent a nurse to their homes to collect.  
24 And from that collection, we calculate concentration and  
25 we had the volume, so we can then take all these

**Polymopoulos**

1 measurements and then plot and then calculate exactly that  
2 number.

3 **THE COURT:** Okay. So, then, when you conduct a  
4 test like this and you measure somebody's sleep duration,  
5 how do you do that?

6 **THE WITNESS:** In that study, sleep duration was  
7 reported on a daily diary through a daily diary voice  
8 system on the phone, where they called every morning and  
9 they told us all the sleep episodes during the night and  
10 the same thing during the day.

11 **THE COURT:** So when you say "all the sleep  
12 episodes during that night," what does that mean?

13 **THE WITNESS:** So if I recall the questions  
14 broken down, that if you slept between 11:00 and 3:00, you  
15 record that. And if you got up and went back to bed from  
16 5:00 to 9:00, you recorded that.

17 So these dark lines that shifted to indicate  
18 the sleep episode, some of them were broken. Others had a  
19 part at night and others during the day, because they  
20 recorded nap episodes of different durations.

21 **THE COURT:** But you are relying on the patient  
22 to tell you, if I'm lying in bed for four hours, how much  
23 of that is sleep and how much is not?

24 **THE WITNESS:** Correct.

25 **THE COURT:** And they are not recording it on

**Polymoropoulos**

1 the telephone until they wake up the next morning?

2 **THE WITNESS:** Correct.

3 **THE COURT:** So if they went to bed at 9:00 p.m.  
4 and they got up at 7:00 a.m., they were in bed. In terms  
5 of measuring how much time they were asleep versus they  
6 weren't, you're relying on the patient's recall?

7 **THE WITNESS:** Correct. And this is the closest  
8 validated system to conduct the studies. That's why we  
9 are saying confounding. Because, of course, they're  
10 confounders of the report.

11 However, in this study, the amount of phase --  
12 with the phase of the cycle you are at. So there is a  
13 good correlation not complete. A good correlation between  
14 these reports so that less amount of nighttime sleep and  
15 more naps happen when the acrophase is during the day,  
16 instead of the night.

17 **THE COURT:** All right. Thank you.

18 You may step down. Thank you.

19 **MR. GROOMBRIDGE:** Your Honor, Vanda's next  
20 witness is Dr. Daniel Combs. And my colleague,  
21 Mr. Daniel Klein, will be presenting this witness.

22 **MR. KLEIN:** Your Honor, may we approach?

23 **THE COURT:** Sure.

24 **THE CLERK:** Please state and spell your name  
25 for the record.

~~Combs~~ Direct

**THE WITNESS:** D-A-N-I-E-L, C-O-M-B-S.

DANIEL COMBS, having been called as a witness, being first affirmed or duly sworn under oath, testified as follows:

**MR. STONE:** Your Honor, may I approach and take the Polymeropoulos binders away so that there's space?

**THE COURT:** Yes.

**MR. STONE:** Thank you.

DIRECT EXAMINATION

**BY MR. KLEIN:**

**Q.** Good afternoon, Dr. Combs.

**A.** Good afternoon.

**Q.** Can you state your name for the record, please?

**A.** Yes, Daniel Combs.

**Q.** And can you pull the microphone up?

**THE COURT:** You can't. It's stuck to the table.

**THE WITNESS:** I can lean a little bit forward.

**THE COURT:** Okay.

**BY MR. KLEIN:**

**Q.** What do you do for a living?

**A.** I'm a sleep medicine physician. Also I'm assistant professor at the University of Arizona.

**Q.** Can you turn to PTX- 823 in your binder, please.

What is this document?

~~Combs~~ Direct

1       **A.**     This is my CV.

2       **Q.**     And you prepared this CV?

3       **A.**     Yes.

4                   **MR. KLEIN:**   Your Honor, I'd like to offer  
5     PTX- 823 into evidence.

6                   **MR. PICKARD:**   No objection.

7                   **THE COURT:**   All right.  It's admitted.

8                   (PTX-823 is admitted into evidence.)

9       **BY MR. KLEIN:**

10       **Q.**     If you look at the bottom, towards the bottom of  
11     Page 100, Chronology of Employment, it says:  Assistant  
12     Professor of Medicine.

13                 Do you see that, Doctor?

14       **A.**     Yes.

15       **Q.**     What do you do as an assistant professor of medicine?

16       **A.**     So assistant professor of medicine in pediatrics.  I  
17     split my time approximately half doing research and  
18     teaching, and the other half doing clinical care for sleep  
19     medicine.

20       **Q.**     And what kind of things do you teach?

21       **A.**     I predominantly teach sleep medicine-related topics.  
22     And so that would include having medical students,  
23     residents, fellows in my sleep medicine clinic.  I give  
24     lecturing regarding sleep medicine.  I also do some  
25     teaching related to research programs for medical

1 students.

2 Q. And when you say "sleep medicine," what does that  
3 encompass? What are you referring to?

4 A. So sleep medicine broadly, really any kind of  
5 disorders relating to sleep. And so I usually say,  
6 reasons people who come to my clinic is they can't sleep,  
7 they sleep too much or a few other reasons.

8 But in general, medical condition that disturbs  
9 sleep, they come to see me for it.

10 Q. And you referred to your research. Is your research  
11 also on the topic of sleep medicine?

12 A. Yes.

13 Q. What types of things have you researched?

14 A. I have current NIH funding looking at clinical trials  
15 for medications for obstructive sleep apnea. I also have  
16 prior research funding from the American Academy of Sleep  
17 Medicine Foundation. And I've published on a wide variety  
18 of sleep topics, so things like sleep apnea, insomnia,  
19 circadian rhythm disorders.

20 Q. And also on Page 1 of your CV, it says: Director  
21 Pediatric Sleep Medicine Program.

22 Do you see that?

23 A. Yes.

24 Q. What do you as a director in the pediatric sleep  
25 medicine program?



1     **A.**    So that's my clinical role, and so that is split,  
2     seeing patients in the sleep medicine clinic and reading  
3     sleep studies.

4     **Q.**    And what kind of sleep disorders have you treated?

5     **A.**    I think most of them, if not at all of them.  So  
6     things like sleep apnea is very common.  Insomnia,  
7     circadian rhythm disorders, they are especially common in  
8     adolescence.

9     **Q.**    What kind of circadian rhythm disorders have you  
10    treated?

11    **A.**    Predominantly delayed sleep phase syndrome.  And --  
12    as that's very common in teenagers.  I've also treated  
13    Non-24.

14    **Q.**    And do you have any experience using tasimelteon?

15    **A.**    Yes.

16    **Q.**    Or administering it?

17    **A.**    Yes.

18           **MR. KLEIN:**  Your Honor, at this time, I would  
19    like to offer Dr. Combs as an expert in sleep medicine and  
20    circadian rhythm and sleep disorders and the treatment  
21    thereof.

22           **MR. PICKARD:**  No objection.

23           **THE COURT:**  All right.

24    **BY MR. KLEIN:**

25    **Q.**    You mentioned a moment ago, Doctor, that you've

~~Combs~~ Direct

published on Non-24; is that correct?

A. Yes.

Q. Can you turn to JTX- 165 in your binder, please?

A. Yes.

Q. What is this?

A. This is the case report that we published on Non-24.

Q. Is this paper something you reviewed in preparing for your testimony today?

A. Yes, it is.

MR. KLEIN: Your Honor, I'd like to offer JTX- 165 into evidence.

MR. PICKARD: No objection.

THE COURT: All right. It's admitted.

(JTX-165 is admitted into evidence.)

BY MR. KLEIN:

Q. What's the purpose of a paper like this?

A. So a case report like this is usually to educate and spread awareness and teach physicians.

Q. Did you prepare a slide addressing some of the details from this case report you think are relevant to the testimony you plan on giving today?

A. Yes.

MR. KLEIN: Mr. Weir, can you pull up PTX- 4.3?

BY MR. KLEIN:

Q. Is this the slide you prepared, Doctor?

1       **A.**     Yes.

2       **Q.**     And what was this case report about?

3       **A.**     So this was a 17-year-old young woman who presented  
4       to our clinic. She was totally blind, had chronic  
5       insomnia that was waxing and waning. She had seen an  
6       outside physician, and I think a sleep physician as well,  
7       who had tried melatonin as well as several sedative  
8       medications such as Ambien, without improvement.

9               So we saw her because she was blind. And insomnia  
10       would kind of come and go in a cyclic manner. We were  
11       very suspicious for Non-24, so we initially started her on  
12       melatonin. At follow-up, about three months later, that  
13       was not successful.

14              So that point in time, we started tasimelteon, which  
15       about three or four months later, she followed up and her  
16       condition had improved and her sleep time had stabilized.

17       **Q.**     And did you prepare a summary of the opinions you  
18       intend to offer today?

19       **A.**     Yes.

20              **MR. KLEIN:** Mr. Weir, can you please pull up  
21       PTX- 4.4.

22       **BY MR. KLEIN:**

23       **Q.**     Is this the slides you prepared, Doctor?

24       **A.**     Yes.

25       **Q.**     And what are you showing us on this slide?

1     **A.**    So my first opinion is that defendants induce  
2     infringement of the Claim 3 of the RE604. It proposed  
3     labels would instruct and promote that prescribers  
4     practice method.

5           Similarly, Number 2, defendants induce infringement  
6     of Claim 14 of the '829 patent, as well as Claim 4 of the  
7     '910 patent. Defendant proposed labels that would  
8     instruct and encourage practicing the methods of those  
9     claims.

10          Finally, similarly, prescribers following the Hetlioz  
11     label would also practice those claims.

12     **Q.**    Did you also prepare a set of slides to assist you  
13     with your testimony on these issues?

14     **A.**    Yes.

15     **Q.**    Can you turn to JTX- 028 in your binder, please?

16     **A.**    Yes.

17     **Q.**    And what is this?

18     **A.**    This is the current Hetlioz label.

19     **Q.**    And you reviewed this label in preparing for your  
20     testimony today?

21     **A.**    Yes.

22     **Q.**    Can you turn to JTX- 027, please?

23     **A.**    Yes.

24     **Q.**    And what is this?

25     **A.**    This was the immediately preceding Hetlioz label.

~~Combs~~ Direct

1 Q. And what's the difference between these two labels?

2 A. So between these two labels, there's the addition of  
3 an indication for Smith-Magenis syndrome, and the oral  
4 suspension used to treat Smith-Magenis syndrome. It is a  
5 rare genetic condition.

6 Q. Is any of the information in the current Hetlioz  
7 label about Smith-Magenis syndrome or the oral suspension  
8 relevant to the opinions you plan on offering today?

9 A. No.

10 MR. KLEIN: Your Honor, at this time, I'd like  
11 to offer JTX- 027 into evidence.

12 MR. PICKARD: No objection.

13 THE COURT: All right. It's admitted.

14 (JTX-027 is admitted into evidence.)

15 BY MR. KLEIN:

16 Q. And, Doctor, can you turn to JTX- 030 in your binder,  
17 please.

18 A. Yes.

19 Q. And what is this?

20 A. This is the Teva proposed generic tasimelteon label.

21 Q. And did you review this label in preparing for your  
22 testimony today?

23 A. Yes.

24 Q. Can you, then, turn to JTX- 033, please.

25 A. Yes.

~~Combs~~ Direct

1 Q. What is this?

2 A. This is the proposed Apotex label for the generic  
3 tasimelteon.

4 Q. And did you review this label as well in preparing  
5 for your testimony today?

6 A. Yes.

7 Q. And are there any material difference between the  
8 Teva and Apotex labels that are relevant to the opinions  
9 you plan on giving today?

10 A. No.

11 Q. And how about as between the defendants' two labels  
12 and the Hetlioz label, are there any differences between  
13 those that you're aware of?

14 A. In regards to Non-24, no. Just the separate  
15 indication for Smith-Magenis.

16 MR. KLEIN: Your Honor, at this time, I'd like  
17 to offer JTX- 030 and 033 into evidence.

18 MR. PICKARD: No objection.

19 THE COURT: All right. They're admitted.

20 (JTX-030 and JTX-033 are admitted into evidence.)

21 BY MR. KLEIN:

22 Q. Finally, Doctor, if you could turn to JTX- 001 in  
23 your binder, please.

24 A. Yes.

25 Q. And what is this?

~~Combs~~ Direct

1     **A.**    This is the RE604 patent.

2     **Q.**    Is this one of the patents that you analyzed in  
3     preparing for your testimony today?

4     **A.**    Yes.

5     **Q.**    Can you turn to JTX- 003, please.

6     **A.**    Yes.

7     **Q.**    What is this?

8     **A.**    This is the '829 patent.

9     **Q.**    Is this also one on the patents you analyzed in  
10    preparing for your testimony today?

11    **A.**    Yes.

12    **Q.**    Thanks.

13           And can you turn to JTX- 004, please.

14    **A.**    Yes.

15    **Q.**    What is this?

16    **A.**    This is the '910 patent.

17    **Q.**    Did you analyze this patent in preparing for your  
18    testimony today?

19    **A.**    Yes.

20           **MR. KLEIN:** Your Honor, I would like to offer  
21    JTX- 003 and JTX- 004 into evidence.

22           **MR. PICKARD:** No objections.

23           **THE COURT:** They are admitted, then.

24           **MR. KLEIN:** Thank you.

25           (JTX-003 and JTX-004 are admitted into evidence.)

~~Combs~~ Direct

1 BY MR. KLEIN:

2 Q. So let's talk about the first claim, Doctor, that you  
3 said you were going to analyze, the RE604 patent, Claim 3.

4 MR. KLEIN: And, Mr. Weir, can you pull up  
5 PDX- 4.6.

6 BY MR. KLEIN:

7 Q. Dr. Combs, what are we looking at here?

8 A. This is the language of that claim.

9 Q. And why did you highlight the three?

10 A. So three is highlighted -- so three is the claim  
11 we'll be discussing. Claim 3 is dependent upon Claims 1  
12 and 2. My understanding is that you need to practice all  
13 of the language.

14 Q. Do you understand which part of this claim language  
15 is what's referred to as the "preamble"?

16 A. Yes.

17 Q. And what part is that?

18 A. That's starting at Number 1, going to the colon after  
19 "comprising."

20 Q. And you're aware that the Court has construed some of  
21 the terms that appear in this claim in this case?

22 A. Yes.

23 Q. Did you provide a slide summarizing those  
24 constructions?

25 A. Yes.



1                   **MR. KLEIN:** Mr. Weir, can you please pull up  
2 PDX- 4.7.

3 **BY MR. KLEIN:**

4 **Q.** Is this the summary you prepared, Dr. Combs?

5 **A.** Yes.

6 **Q.** And did you apply these constructions in forming your  
7 opinions in this case?

8 **A.** Yes, I did.

9 **Q.** And how did the Court construe the entraining term?

10 **A.** Entraining meant synchronizing.

11 **Q.** And you see at the top, the top two rows -- or the  
12 top row, rather, it says: The preambles are limiting?

13 **A.** Yes.

14 **Q.** Do you understand what that means?

15 **A.** Yes. That means the language in the preamble needs  
16 to be addressed.

17 **Q.** And are you aware the parties have offered  
18 definitions of what they consider to be a person of  
19 ordinary skill in the art?

20 **A.** Yes.

21 **Q.** Did you prepare a slide summarizing those?

22 **A.** Yes.

23 **MR. KLEIN:** Mr. Weir, can you pull up PDX- 4.8.

24 **BY MR. KLEIN:**

25 **Q.** Dr. Combs, what is Vanda's definition of a person of

1 ordinary skill in the art?

2 **A.** So Vanda's definition is a person, or team of people,  
3 with experience treating individuals with circadian rhythm  
4 disorders, including a person or persons qualified to  
5 prescribe medication; or alternately, a person or persons  
6 with experience researching circadian rhythm disorders.

7 **Q.** Did you apply that definition in forming your  
8 opinions as to Claim 3 of the RE604 patent.

9 **A.** Yes.

10 **Q.** And you understand that there are some differences  
11 between Vanda's definition of a person of ordinary skill  
12 in the art and the defendants'?

13 **A.** Yes.

14 **Q.** Do any of those differences impact or alter any of  
15 the opinions you plan on offering today?

16 **A.** No.

17 **Q.** Do you qualify as a person of ordinary skill under  
18 either or both of these definitions?

19 **A.** I believe I qualify under both.

20 **Q.** Did you prepare a slide summarizing the elements of  
21 Claim 3 of the RE604 patent, the patent that you plan on  
22 addressing today?

23 **A.** Yes.

24 **MR. KLEIN:** Mr. Weir, can you please pull up  
25 PDX- 4.9.

1 BY MR. KLEIN:

2 Q. Is this the summary you prepared?

3 A. Yes.

4 Q. And what are we looking at here?

5 A. So these are all the elements pulled out of Claim 3.  
6 And so I just wanted to address all of these one by one.

7 Q. Let's go to the first element.

8 MR. KLEIN: Mr. Weir, can you please pull up  
9 PDX- 4.10.

10 BY MR. KLEIN:

11 Q. What are we looking at here, Dr. Combs?

12 A. So these are the sections in the drug label that  
13 would lead a practitioner to follow the elements of the  
14 claim. Because I can address all the sections one by one.

15 Q. And when you refer to the drug label, you're  
16 referring to the defendants' labels?

17 A. Yes.

18 Q. And before we move on, what do you mean when you  
19 refer to -- what is a drug label?

20 A. So a drug label is instructions or a guide to  
21 prescribers on how to use the medication.

22 Q. And who is the intended audience of a drug label?

23 A. Whoever is prescribing. So in this case, sleep  
24 medicine physicians.

25 Q. Okay. Let's go on to the first section.

1                   **MR. KLEIN:** Mr. Weir, can you please pull up  
2 the next slide?

3                   **BY MR. KLEIN:**

4                   **Q.** How is this section of the defendants' label relevant  
5 to your opinion on the entraining element from Claim 3 of  
6 the RE604 patent?

7                   **A.** Section 1 is discussing Tasimelteon for treatment of  
8 Non-24. The disorder of Non-24 is a lack of entrainment.  
9 And so to treat Non-24, a goal would be to entraining the  
10 patient.

11                   **Q.** And so how is this language relevant to your opinion  
12 that defendants will induce infringement of the entraining  
13 element from Claim 3 of the reissue patent?

14                   **A.** So sleep medicine physicians would understand this  
15 section's promoting entrainment of a patient with Non-24.

16                   **Q.** Let's go to the next section.

17                   So how are -- how is Section 2.2 and 2.4 relevant to  
18 your opinion on the entraining element from Claim 3?

19                   **A.** So in Section 2.2, the language, the 20 milligrams an  
20 hour before bedtime at the same time every night, and then  
21 similarly with 2.4, if they are unable to take tasimelteon  
22 on the same time on a given night, patients skip that  
23 dose, take the next dose as scheduled. This is due to  
24 entrainment.

25                   And so tasimelteon functions like an anchor for your

1 circadian rhythm.

2 So people with Non-24 have a progressive delay. And  
3 so periodically, they're -- their night is occurring in  
4 our day. And then sometimes their in days, where their  
5 night -- our night and they sleep better.

6 So the goal is they take it the same time every night  
7 to anchor that circadian rhythm, which is entrainment.

8 **Q.** And so how is this language relevant to your opinion  
9 that defendants will induce infringement of the entraining  
10 element?

11 **A.** So this language is giving -- is promoting giving  
12 tasimelteon at the same time, the hour before bedtime  
13 every night, in order to promote entrainment.

14 **Q.** Okay. Let's move on to the next section in the  
15 label.

16 How is Section 14.1 relevant to your opinion on  
17 the -- about the entraining element?

18 **A.** Section 14.1 is discussing the clinical trial  
19 results. And so in this study, they're discussing that  
20 when patients were treated with tasimelteon, for that  
21 20 milligrams an hour before bedtime at the same time  
22 every night, this led to their melatonin acrophase, so  
23 that the time their melatonin peaked every night was  
24 occurring at the same time of day.

25 So, again, with Non-24, typically you would see in

1 untreated Non-24 a progressive delay, which means they are  
2 not entrained with the 24-hour day. When their melatonin  
3 acrophase is occurring at the same time every day, that's  
4 evidence of entrainment.

5 **Q.** And so how is this language being in the label, in  
6 your opinion, relevant to whether defendants will induce  
7 infringement of the entraining element from Claim 3 of the  
8 reissue patent?

9 **A.** Prescribers would understand that if you're giving  
10 tasimelteon as directed, it's going to lead to  
11 entrainment. It's going to promote entrainment.

12 **Q.** And then let's go to the next slide.

13 And so on the screen, you have Table 3 from  
14 Section 14.1 of the label. How is this section relevant  
15 to your opinion on the entraining element?

16 **A.** So this is the Quartile metrics that were mentioned  
17 earlier. So one of the concepts that's Non-24 is  
18 periodically you sleep totally fine. And so if you look  
19 at a metric, like just total sleep time, it's not very  
20 helpful.

21 And so that's why when you look at that, they're  
22 looking at nighttime sleep time on most symptomatic  
23 nights, and then also how much they have fallen asleep  
24 during the daytime on most symptomatic nights because a  
25 period of that time will be normal.

~~Combs~~ Direct

1 And so what you can see is in Study 1, patients were  
2 analyzed to start tasimelteon. And so you can see is --  
3 when they're treated with tasimelteon, they basically move  
4 an hour of sleep from the daytime to nighttime.

5 And then Study 2, where patients are analyzed to stay  
6 on tasimelteon or stop tasimelteon, if they stayed on  
7 tasimelteon, there's really no change. If they stopped  
8 tasimelteon, that hour of sleep kind of moved from the  
9 nighttime to daytime.

10 So that consolidation of sleep at night is evidence  
11 of entrainment.

12 **Q.** And so how does this section of the defendants' label  
13 is relevant to your opinion about whether they will induce  
14 infringement of the entraining element from Claim 3 of the  
15 reissue patent?

16 **A.** Prescribers would understand. But this is -- it's  
17 promoting entrainment.

18 **Q.** Let's move on to the next element, daily sleep period  
19 of approximately seven-to-nine hours.

20 Dr. Combs, what are we looking at here?

21 **A.** So this is the language on daily sleep period in the  
22 claim.

23 **Q.** And did you prepare -- do you understand that the  
24 parties have different interpretations of what "daily  
25 sleep period" term means, correct?

1       **A.**    Yes.

2       **Q.**    Did you prepare a slide summarizing those  
3       differences?

4       **A.**    Yes.

5       **Q.**    So is this a slide you prepared, Doctor?

6       **A.**    Yes.

7       **Q.**    So what is Vanda's interpretation of the daily sleep  
8       period limitation?

9       **A.**    It's a window of approximately seven-to-nine hours  
10       that starts at target bedtime, and then ends at about  
11       target wake time. And so patients consolidate their daily  
12       sleep. And so with that -- so that's like sleep  
13       opportunity.

14       So within sleep medicine, there is a concept of total  
15       sleep time. So how much are you asleep. Like how much  
16       are you actually asleep versus sleep opportunity, which is  
17       more how much time are you in bed trying to sleep.

18       **Q.**    Do you agree with this interpretation?

19       **A.**    Yes.

20       **Q.**    And what's your understanding of defendants'  
21       interpretation of the "daily sleep period" term?

22       **A.**    I believe the primary difference, I believe both  
23       sides agree that a seven- to nine-hour period, which is  
24       kind of the standard sleep recommendation for how much  
25       time you should be attempting to sleep. My understanding



1 is that their definition requires you should be asleep for  
2 almost that entire period.

3 Q. And in the context of treating someone with Non-24,  
4 why do you think defendants' interpretation is incorrect?

5 A. I think they are using more total sleep time rather  
6 than sleep opportunity. So I don't think there's any  
7 expectation that someone is asleep continuously for  
8 seven-to-nine hours.

9 Q. And why would a target wake time follow a daily sleep  
10 period of approximately seven-to-nine hours in someone who  
11 is being treated for Non-24?

12 A. So if you have a target bedtime and you know you are  
13 going to be in bed for a set amount of time, the target  
14 wake time would then follow.

15 So I know that at 10:00, and I'm going to be in bed  
16 for eight hours, then my wake time must be 6:00.

17 Q. And would that be true for someone with Non-24 who is  
18 entrained?

19 A. Yes.

20 Q. And you were here for Mr. Coblentz's opening  
21 statement, correct?

22 A. Yes.

23 Q. Did you see him put up a slide that had the title:  
24 Sleeping seven-to-nine hours?

25 A. Yes.

~~Combs~~ Direct

1 Q. As a sleep medicine physician, do you agree that a  
2 daily sleep period of seven-to-nine hours is synonymous  
3 with sleeping for seven-to-nine hours?

4 A. No.

5 Q. Why not?

6 A. People don't -- so when you go to bed and when you  
7 fall asleep aren't necessarily the same time. So, for  
8 example, if I go to bed at 10:00, and I take 15 minutes to  
9 fall asleep, I wake up over the night for an hour because  
10 one of my kids wakes me up, and then I go back to sleep,  
11 fall back asleep, and then get up at 6:00, I would say  
12 that I had a sleep window of about eight hours, but I  
13 might have only slept five and a half.

14 So it's not reality-based. People don't just fall  
15 asleep and sleep continuously until the next morning.  
16 Even if they don't remember, there's brief wake-ups. So  
17 it's not reality-based.

18 Q. Are there statements in the RE604 patent that you  
19 believe support your interpretation of the daily sleep  
20 period?

21 A. Yes.

22 MR. KLEIN: Mr. Weir, can you please pull up  
23 PDX-4.18.

24 BY MR. KLEIN:

25 Q. Dr. Combs, why are you showing us the first block of

1 text?

2 **A.** So in this first block of text, they discuss daily  
3 sleep period. As you can see that they define this as  
4 daily sleep period approximately seven-to-nine hours. And  
5 then you can see in parenthesis: Understanding, of  
6 course, the patient may not actually sleep during the  
7 entire sleep period.

8 So they are clearly not saying that you should be  
9 sleeping seven-to-nine hours.

10 **Q.** And how about the second box, how is that relevant --  
11 or how does that support your interpretation of daily  
12 sleep period?

13 **A.** So this is kind of a more concrete example. So if  
14 someone goes to bed at 10:30 and they woke up at 6:30,  
15 that would be a sleep period of eight hours. However, you  
16 will notice that they self-reported a total sleep time of  
17 five hours.

18 **Q.** And then the last box I see you highlighted the text  
19 in a different color.

20 Why are you showing us this text?

21 **A.** So "nighttime total sleep time" is the phrase that  
22 you would use when you're talking about how much someone  
23 actually slept. And this is kind of a standard phrasing;  
24 like total sleep time is, like, how many minutes you  
25 actually slept.

~~Combs~~ - Direct

1 Q. Okay.

2 MR. KLEIN: Mr. Weir, can you please put up  
3 PDX-4.19.

4 BY MR. KLEIN:

5 Q. Dr. Combs, what are we looking at here?

6 A. So these are all of the sections of the label that  
7 supports the prescriber's practice of the claims.

8 Q. And I see you grayed out some of the sections here.

9 A. Yes.

10 Q. Why did you do that?

11 A. So Sections 1, 2.4 and the part about the peak  
12 melatonin, I already discussed as related to entrainment.  
13 Because those are going to lead to entrainment, those are  
14 going to lead to consolidating your sleep and your  
15 nighttime sleep period.

16 Q. Let's go to the first additional section you want to  
17 address.

18 MR. KLEIN: Mr. Weir, can you please pull up  
19 PDX-4.20.

20 BY MR. KLEIN:

21 Q. How is this section of the label relevant to your  
22 opinion on the daily sleep period element, Doctor?

23 A. So this is discussing that symptoms of nighttime  
24 sleep disruption and daytime sleepiness are cyclical in  
25 patients of Non-24. So Non-24, the key issue isn't how

1 much sleep they get, it's when the sleep is. And so your  
2 goal is -- those two can run together. And so your goal  
3 is really more moving your sleep towards a consolidated  
4 period which would be in the night unless you are a shift  
5 worker.

6 **Q.** And so how is this language relevant to your opinion  
7 that defendants will induce infringement of the daily  
8 sleep period claim element?

9 **A.** So this would promote consolidating that sleep in  
10 that daily sleep period.

11 **MR. KLEIN:** And Mr. Weir, can you pull up the  
12 next slide.

13 **BY MR. KLEIN:**

14 **Q.** See here again, we have Table 3 from Section 14.1,  
15 Doctor.

16 How is this section relevant to your opinion on the  
17 daily sleep period element?

18 **A.** So similar concepts. And on 14.1 again, the patients  
19 are moving their sleep from the daytime to the nighttime.  
20 So they are consolidating their sleep into their nighttime  
21 sleep period.

22 **Q.** And how is this language relevant to your opinion  
23 that the defendants will induce infringement of the daily  
24 sleep period element?

25 **A.** This will promote consolidating that sleep into the

~~Combs~~ Direct

1 daily sleep period.

2 Q. Let's go to the next section.

3 Dr. Combs, why is Section 2.2 relevant to your  
4 opinion on whether defendants will induce infringement of  
5 the daily sleep period element?

6 A. So this is discussing taking tasimelteon an hour  
7 before bedtime at the same time every night. And so if  
8 you are taking tasimelteon at the same time every night an  
9 hour before bedtime, it follows you are going to have  
10 bedtime an hour later. You are going to have your sleep  
11 period of seven-to-nine hours and then your wake time is  
12 after that because that's what would happen.

13 Q. And so how do we establish the target wake time  
14 aspect of this claim element from this language?

15 A. So your target wake time is inherently going to  
16 follow. So if you take tasimelteon at a set time, then an  
17 hour later you go to bed, after you sleep for  
18 seven-to-nine hours, your wake time is going to be the  
19 next thing that happens.

20 Q. Let's go on to the next claim element.

21 THE COURT: Why don't we take a break. Let's  
22 do that.

23 (Whereupon, a recess was taken.)

24 BY MR. KLEIN:

25 Q. Dr. Combs, I was just about to move on to the next

1 element of Claim 3 of the reissue patent.

2 **MR. KLEIN:** Mr. Weir, can you please pull up  
3 PDX-4.24.

4 **BY MR. KLEIN:**

5 **Q.** And Dr. Combs, how are Section 2.2 and 14.1 relevant  
6 to the element maintaining said 24-hour sleep-wake cycle  
7 from Claim 3 of the reissue patent?

8 **A.** Section 2.2 is, again, discussing at the same time.  
9 So maintaining that tasimelteon at the same time every  
10 night will maintain that set, consistent 24-hour  
11 sleep-wake cycle. And then similarly in Section 14.1 when  
12 they are discussing the part about the peak melatonin  
13 acrophase, that's describing a melatonin equivalence of  
14 maintaining that 24-hour sleep-wake cycle. So that is  
15 maintaining that 24 hours sleep-wake cycle.

16 **Q.** And the second set of highlighted language in the  
17 14.1 section, what is that referring to again?

18 **A.** So that's referring to individuals who are with  
19 Non-24 and not treated, they are going to have that delay  
20 typically. So they are not having -- so they have a  
21 progressive delay in their sleep time as opposed to a set  
22 24-hour schedule.

23 **Q.** Let's go to the next element. Orally administering  
24 to the patient 20 milligrams of tasimelteon.

25 Dr. Combs, did you prepare a slide identifying the

~~Combs~~ Direct

1 sections of the label that you think are relevant to this  
2 element?

3 **A.** Yes.

4 **MR. KLEIN:** Mr. Weir, can you, please, pull up  
5 PDX-4.26.

6 **BY MR. KLEIN:**

7 **Q.** And Dr. Combs, what are we looking at here?

8 **A.** So Section 2.2 is saying the dose is 20 milligrams.  
9 And then Section 11, there's a slight difference between  
10 the tasimelteon Teva label. They mean the same thing  
11 discussing it's 20-milligram capsules oral administration  
12 or intended for oral administration. And then finally,  
13 Section 14.1, again, the dose is 20 milligrams.

14 **Q.** Thank you. Let's go on to the next element.

15 Patient is totally blind. And did you also prepare a  
16 slide identifying the sections from the defendants' labels  
17 that you think are relevant to this element?

18 **A.** Yes.

19 **MR. KLEIN:** Mr. Weir, can you, please, pull up  
20 PDX-4.28.

21 **BY MR. KLEIN:**

22 **Q.** Dr. Combs, what are we looking at here?

23 **A.** So Section 1.1, again, tasimelteon is for the  
24 treatment of Non-24. Because the light is the main cue  
25 that sets your circadian rhythm, people who are blind are



~~Combs~~ Direct

1 much, much, much more likely to have Non-24. And so  
2 prescribers would understand that Non-24 is predominantly  
3 a disorder seen in people who are blind.

4 Section 14.1 discusses the clinical trials where it's  
5 specifically in totally blind patients with Non-24. And  
6 so prescribers would understand that the label is  
7 promoting the use of tasimelteon in totally blind  
8 patients.

9 **Q.** Thank you. Let's go on to the next element, 0.5 to  
10 1.5 hours before the target bedtime.

11 Did you also prepare a slide identifying the relevant  
12 sections of the defendants' labels for this element?

13 **A.** Yes.

14 **MR. KLEIN:** Mr. Weir, can you please put up --

15 **THE COURT:** Can I ask you something?

16 **MR. KLEIN:** Yes.

17 **THE COURT:** Did you all meet and confer? How  
18 much of this is going to be disputed?

19 **MR. PICKARD:** For the '604 patent, we are  
20 challenging the entrainment limitation and the seven- to  
21 nine-hour 24-hour wake cycle.

22 **THE COURT:** I mean, almost I would say it's  
23 worth taking a break. Because I don't know why I have to  
24 go through all these claim limitations if at the end of  
25 the day -- because this boils down to two things, or three

1 things. And even if it's ten things, did you meet and  
2 confer, have you discussed this so that I know what you  
3 know?

4 **MR. STONE:** Your Honor, I think it is clear  
5 from the openings that the only disputed issues for this  
6 claim term are entrainment and the seven- to nine-hour  
7 sleep period.

8 **THE COURT:** I mean, that's what I thought. I  
9 thought I'm going to have a trial that's going to be so  
10 focused on two claim limitations.

11 **MR. STONE:** In the absence of a stipulation, we  
12 thought we would simply establish it. But why don't we  
13 talk to the plaintiffs about whether we -- the defendants  
14 about whether we can stipulate to the other elements.

15 That seems to make sense, Your Honor.

16 **THE COURT:** I have really good lawyers on both  
17 sides of this case. I've made that comment, really good  
18 lawyers, among my favorite lawyers. I see a lot of repeat  
19 players.

20 I mentioned this is my ninth trial since  
21 October 25th. I've already got three bench trial opinions  
22 I've got to get out. I just can't do all this for sport,  
23 especially when we have really good lawyers.

24 And I'm sensing this case is boiling down to a  
25 handful of issues. I mean, I do think it's incumbent upon

1 the lawyers, and we have very good Delaware counsel here,  
2 too. We should be talking about these things in an ANDA  
3 case. What has to be litigated?

4 You guys I went off the record with after the  
5 pretrial and talked about how crazy our calendar is and  
6 what we need to do. I'm kind of a little astounded that  
7 we didn't get through this and figure this out before I'm  
8 sitting here. And I mean, you know, you did work together  
9 and reached some compromise, some claims went away.

10 But I've got better things to do than sit  
11 through an hour of let's just go through all these claims  
12 if this is absolutely meaningless. Now, maybe it is not,  
13 you know, and maybe you want some time to go discuss it,  
14 but I would think you guys on the defense side would know  
15 what you are contesting about this.

16 I mean, totally blind? Are we going to have a  
17 debate on whether there is a totally blind limitation met?

18 **MR. STONE:** Not from our side, Your Honor. No.  
19 We think it is obviously met, and I don't think they have  
20 an expert who will say otherwise.

21 **MR. ROZENDAAL:** No, that is not a limitation  
22 that we are fighting about, Your Honor.

23 **MR. GROOMBRIDGE:** Your Honor, we'd be happy to  
24 take a break and see -- you know, if we take 20 minutes,  
25 maybe we can work out something. As Your Honor is aware,

~~Combs~~ Direct

1       there's often details the lawyers are all anxious about.  
2       But I think we have a good-enough working relationship  
3       that we could figure this out and reduce it to writing in  
4       a way that we are not going to need to -- that would cut  
5       through a lot of this.

6               **MR. ROZENDAAL:** We're certainly open to trying  
7       to streamline the presentation, Your Honor.

8               **THE COURT:** What's the efficient way to resolve  
9       it? You think take a break for 15 minutes? You know,  
10      what do we need to do? Because this isn't efficient for  
11      me because it's hard for me to go work on an opinion when  
12      I get a 15-minute break as opposed to an hour break.

13              **MR. STONE:** I think that we are probably 60  
14      seconds from done with the first patent because this is  
15      the last element of it, so hopefully Your Honor is right  
16      about the superfluousness. It is also done -- maybe it  
17      makes sense for us to confer about the drug-drug  
18      interaction patents and see if we are sure we know what we  
19      are fighting about about those.

20              **MR. KLEIN:** Your Honor, the presentation on the  
21      drug-drug interactions patents, those claims do have  
22      overlapping elements with the reissue patent, and the  
23      discussion is not going to retread that ground. It's just  
24      going to say it was previously discussed.

25              **THE COURT:** All right. Let's continue.

1 From now on, I need you -- you all need to get  
2 together at night, and you really need to say what do we  
3 need, what's important here. For what it's worth, it  
4 takes away from all the stuff that's meaningful, you know,  
5 because I don't know what's a distraction, what I need to  
6 spend real brain power on. I figured I didn't have to  
7 spend brain power on totally blind.

8 **MR. KLEIN:** Your Honor, may I just confer  
9 with --

10 **THE COURT:** Yes, go ahead.

11 But I've got to say, I'm killing myself that I  
12 gave you 13 hours each, just killing myself.

13 You know, to counsel, this is the most I have  
14 given in an ANDA case. And you all, depending on your  
15 reputations, I let it go. I should have cut it back. I'm  
16 tempted to say 11 each. So you need to confer and figure  
17 it out because this is a waste of time.

18 **MR. KLEIN:** Is it okay to proceed, Your Honor?

19 **THE COURT:** Yes.

20 **BY MR. KLEIN:**

21 **Q.** We're going to skip this one, Dr. Combs.

22 And then if you could just -- what is your ultimate  
23 conclusion as to whether or not defense will induce  
24 infringement of Claim 3 of the RE604 patent?

25 **A.** The labels would induce infringement.

1 Q. So let's move on to the next patent. Claim 14 of the  
2 '829 patent.

3 Dr. Combs, are you aware that the parties have,  
4 again, a definition -- somewhat different definitions of  
5 who a person of ordinary skill in the art is for both the  
6 '829 patent and the next one we will discuss, the '901  
7 patent?

8 A. Yes.

9 Q. Did you prepare a slide summarizing those  
10 interpretations or definitions?

11 A. Yes.

12 MR. KLEIN: Mr. Weir, can you please pull up  
13 PDX-4.33.

14 And the Vanda definition on the left --

15 THE COURT: All right. Hold up. I'm not going  
16 to repeat this again.

17 You dispute the artisan of ordinary skill. Is  
18 it an issue for me to debate? Because every single trial  
19 I've had this. I get this slide and I get the question,  
20 which I know is coming, which is, does it make a  
21 difference, right? You are going to ask him that  
22 question, aren't you?

23 MR. KLEIN: That, and did he apply it.

24 THE COURT: Yeah.

25 Is there a dispute over the relevant artisan of

1 ordinary skill?

2 **MR. ROZENDAAL:** Not on infringement. I think,  
3 I think it could make a difference for invalidity. I  
4 don't think it's going to make a difference for  
5 infringement.

6 **THE COURT:** All right. So, then, let's only  
7 deal with it in invalidity.

8 **MR. KLEIN:** Great.

9 **BY MR. KLEIN:**

10 **Q.** Dr. Combs, what are we looking at here?

11 **A.** This is Claim 14. Again, Claim 14 is dependent on  
12 Claim 13.

13 **Q.** And do you understand which part of this claim is  
14 referred to as the preamble?

15 **A.** 13 to the column after comprising.

16 **Q.** Thank you.

17 Did you prepare a slide summarizing the Court's claim  
18 constructions for this claim?

19 **A.** Yes.

20 **MR. KLEIN:** Mr. Weir, can you please pull up  
21 PDX-4.35.

22 **BY MR. KLEIN:**

23 **Q.** And are these the constructions that you understand  
24 the Court has applied for this patent?

25 **A.** Yes.

~~Combs~~ Direct

1 Q. And did you apply these?

2 A. Yes.

3 Q. And did you also prepare slides summarizing the  
4 elements of Claim 14 of the '829 patent that you plan on  
5 addressing?

6 A. Yes.

7 Q. Quickly, Dr. Combs, why have you put a checkmark next  
8 to the bottom two claim elements?

9 A. The second two were addressed in my discussion of  
10 infringement of the RE604 patent.

11 Q. And so the top portion is the remaining element or  
12 part of the claim that you want to address, correct?

13 A. Yes.

14 MR. KLEIN: Mr. Weir, can you please pull up --

15 THE COURT: Sorry to interrupt. But just one  
16 thing, Doctor.

17 You heard me express frustration about time  
18 management. It doesn't improve the situation when lawyers  
19 and witnesses speak quickly to try to overcome that.  
20 Naturally that's the lawyers, it's not just with the  
21 witnesses, because that's what happens.

22 What we want is a streamlined case where people  
23 speak slowly, so we can pick it up. All right? So you  
24 don't need to rush it, Mr. Klein, in terms of  
25 presentation.



~~Combs~~ Direct

1                   **MR. KLEIN:** Yes, Your Honor.

2                   **THE COURT:** Thank you.

3                   **MR. KLEIN:** Mr. Weir, can you please pull up  
4 PDX-4.37.

5                   **BY MR. KLEIN:**

6                   **Q.** Dr. Combs, what are we looking at here?

7                   **A.** So at the top is the claim. And then you can see in  
8 Section 7.1 the label states: Avoid use of tasimelteon in  
9 combination with fluvoxamine or other strong CYP1A2  
10 inhibitors.

11                   And section 12.3 discusses why that is.

12                   So if you give the combination, you will actually  
13 increase the effective dose the patient receives of  
14 tasimelteon, which could actually make it less effective.

15                   So as we kind of touched on briefly, there's kind of  
16 that effect -- that short, sharp pulse for it to be  
17 effective. And so if you have spillover, you can  
18 actually -- it's no longer effective.

19                   And so prescribers would understand that in order to  
20 avoid the use of tasimelteon in combination with  
21 fluvoxamine, for example, you would want to discontinue  
22 the fluvoxamine prior to starting the tasimelteon.

23                   **Q.** How is this language relevant to your opinion that  
24 the defendants will induce infringement of this claim  
25 element?

~~Combs~~ Direct

1     **A.**    This would instruct prescribers to practice the  
2     claim.

3     **Q.**    How would a prescriber practice these label  
4     instructions that we're looking at in a real-world  
5     scenario?

6     **A.**    So, for example, fluvoxamine can be used for mood  
7     disorders.  So what I would expect is that if you had a  
8     patient with Non-24 on fluvoxamine that you'd want to  
9     start tasimelteon on, you would have them discontinue  
10    fluvoxamine, switch to a different SSRI or other treatment  
11    for mood disorder, and then you'll start the tasimelteon.

12    **Q.**    Thank you.

13           So what is your ultimate conclusion on whether  
14    defendants infringe -- induce infringement of the Claim 14  
15    of the '829 patent?

16    **A.**    That they would induce infringement.

17    **Q.**    Let's go on to the last claim of the last patent.  
18    Claim 4 of the '910 patent.

19           Dr. Combs, what are we looking at here?

20    **A.**    So this is the claim, and it's highlighted for the  
21    same reasoning.  Claim 4 is dependent upon Claims 1, 2,  
22    and 3.

23    **Q.**    And do you understand which part of this claim  
24    language is what we refer to as the claim preamble?

25    **A.**    Yes.  From one to the colon.

1 Q. Thank you.

2 And you understand that the Court has construed some  
3 of the terms that appear in this claim?

4 A. Yes.

5 MR. KLEIN: Mr. Weir, can you please pull up  
6 PDX-4.41.

7 BY MR. KLEIN:

8 Q. Are these the constructions that you applied,  
9 Dr. Combs?

10 A. Yes.

11 MR. KLEIN: Mr. Weir, can you pull up PDX-4.42.

12 BY MR. KLEIN:

13 Q. Dr. Combs, what are we looking at here?

14 A. So these are the elements. Again, I addressed the  
15 first three checked ones in my discussion of the RE604  
16 patent, so I'm only going to discuss the last one.

17 Q. Okay. And the claim element, "the patient is  
18 light-perception impaired," that wasn't in the RE604  
19 patent, correct?

20 A. That's correct. So totally blind is light-perception  
21 impaired.

22 Q. Let's go to the next slide.

23 All right. Dr. Combs, what are we looking at here?

24 A. So at the top is the claim, and then you can see  
25 Section 7.2 instructs subscribers to avoid using

~~Combs~~ Direct

1 tasimelteon in combination with rifampin.

2 And, again, in Section 12.3, they discuss why, which  
3 is if you give the two together, the effective dose the  
4 patient receives of tasimelteon goes down by about  
5 90 percent if you give the two together. And so  
6 prescribers would understand that you'd want to stop  
7 rifampin prior to starting tasimelteon.

8 **Q.** And so how is this language relevant to your opinion  
9 that defendants will induce infringement of this claim?

10 **A.** This would instruct prescribers to follow the claim.

11 **Q.** How would a prescriber practice this label  
12 instructions in a real-world scenario?

13 **A.** So rifampin is an antibiotic, and so typically that's  
14 not something you are on forever. You are on it for a  
15 course of treatment. And so once you complete your course  
16 of treatment, I'd expect you'd then discontinue the  
17 rifampin and start tasimelteon.

18 **Q.** Thank you.

19 So what is your ultimate conclusion as to whether or  
20 not defendants will induce infringement of Claim 4 of the  
21 '910 patent?

22 **A.** They would.

23 **MR. KLEIN:** I have no further questions for the  
24 witness.

25 **THE COURT:** Thank you. Cross.

~~Combs~~ - Cross

CROSS-EXAMINATION

**BY MR. PICKARD:**

**Q.** Good afternoon, Dr. Combs. My name is Byron Pickard. We haven't met, so good to meet you this afternoon.

If we could, I'd like to start with the '604 patent. I will wait a moment for the binders to get handed out. Apologies.

And I'd just like to focus initially our discussion on the entrainment limitation, if we can.

You're aware that in seeking FDA approval for Hetlioz that Vanda sought to obtain a drug label that would include the word "entrainment" in, among other places, the dosage and administration section?

You are aware of that?

**A.** Through my work in the trial, yes.

**Q.** Okay. And if you look in your trial binder there, your cross-exam binder, if you could take a look at Exhibit 139, please.

**MR. PICKARD:** And this is already in evidence, so we can display that, Mr. Brooks.

Thank you.

**BY MR. PICKARD:**

**Q.** If you look at the front page of the label, Dr. Combs, you will see it says: Entrainment of the master body clock by tradename. That's the placeholder for

1 Hetlloz.

2 **A.** Is this DTX-139?

3 **Q.** Yes. Sorry. Let me know when you are there.

4 **A.** Yes.

5 **Q.** Are you familiar with this document?

6 **A.** I don't remember seeing it.

7 **Q.** You didn't consider this in forming your opinions in  
8 this case?

9 **A.** I don't remember.

10 **Q.** Don't remember. All right.

11 Well, you see here -- I mean, you heard Mr. --  
12 Dr. Polymeropoulos testify as to this label earlier today.  
13 You did?

14 **A.** Yes.

15 **Q.** Okay. So you understand this was a label that Vanda  
16 attempted to obtain from FDA but was unsuccessful in doing  
17 so, correct?

18 **A.** Yes.

19 **Q.** Okay. And you see here under the Dosage and  
20 Administration, it reads: Entrainment of the master body  
21 clock by tradename. It may be immediate or it may require  
22 treatment with tradename for one full circadian cycle.

23 Did I say that correctly?

24 **A.** Yes.

25 **Q.** And if you look at Page 11 of the document,

~~Combs~~ - Cross

1 Dr. Combs, under the Clinical Study section, four  
2 paragraphs down, you will see the words "the primary  
3 efficacy measures"?

4 Do you see that?

5 **A.** Yes.

6 **Q.** You are aware that Vanda, as part of its approval  
7 process, attempted to submit or obtain approval based on  
8 primary efficacy measures in the so-called SET study that  
9 were entrainment of circadian rhythms as measured by aMT6s  
10 and clinical response?

11 **A.** Yes.

12 **Q.** And aMT6s, that's the melatonin metabolite, right?

13 **A.** That's correct.

14 **Q.** And according to this label, "clinical response" was  
15 defined as the coincident demonstration of entrainment of  
16 aMT6s and a score on a sleep measure, correct?

17 **A.** Yes. It's not a standard sleep measurement.

18 **Q.** It is not a standard sleep metric, but it is a sleep  
19 metric?

20 **A.** I believe we -- entrainment was included, yeah.

21 **Q.** Well, that's my point. That it had entrainment plus  
22 a sleep measure, correct?

23 **A.** Yes. I don't remember all the metrics from the  
24 Non-24 scale. I don't know if there is a patient quality  
25 of metric, did I feel better.

1 Q. And you understand the FDA did not approve this  
2 label, correct?

3 A. Yes.

4 Q. All right. If we could, let's turn to the label at  
5 JTX-28, please. It's also in your binder.

6 A. Okay.

7 Q. And I'd like you to turn to the Clinical Study  
8 section there, 14.1.

9 A. Yes.

10 Q. I guess as an initial question, I want to make sure  
11 we're clear. In forming your infringement opinions as to  
12 the RE604 patent, you relied on information that's found  
13 in the clinical study section of the Hetlioz defendants'  
14 labels, correct?

15 A. Yes.

16 Q. And if we look at Table 3 in that section, that sets  
17 forth the data for the efficacy endpoints that were  
18 ultimately the basis for FDA approval, correct?

19 A. Yes.

20 Q. And those endpoints in Table 3, they don't include  
21 the melatonin metabolite aMT6, correct?

22 A. No.

23 Q. In fact, the label doesn't mention "entrainment" at  
24 all.

25 A. The concept or the word?



~~Combs~~ - Cross

1 Q. The word.

2 A. No.

3 Q. And the FDA approved label also doesn't use the word  
4 "melatonin circadian rhythm" either, does it?

5 A. I believe no.

6 Q. And cortisol circadian rhythm is another way to  
7 measure entrainment, correct?

8 A. Yes.

9 Q. And the approved label doesn't use the words  
10 "cortisol circadian rhythm" either, correct?

11 A. Correct.

12 Q. And having seen Dr. Polymeropoulos's testimony today,  
13 you are aware that Vanda has instructed its salespeople  
14 not to use the word "entrainment" when discussing Hetlioz  
15 to its customers and physicians, correct?

16 A. Yes.

17 Q. And it's still your opinion that somehow the label  
18 teaches entrainment to prescribers; is that right?

19 A. Yes.

20 Q. During your direct, you said that a goal of  
21 administering Hetlioz to Non-24 patients was to achieve  
22 entrainment. And I want to see if we can agree on  
23 something. Do you agree that in addition to entraining  
24 Non-24 patients, that tasimelteon can also increase total  
25 sleep time per day and reduce total naptime per day?

1       **A.**     In the label?

2       **Q.**     No, just as a general matter, Doctor. Do you agree  
3       that in addition to entraining a Non-24 patient, a  
4       melatonin -- or sorry, tasimelteon can also increase total  
5       sleep time per day and reduce total naptime per day?

6       **A.**     Across the board or do you mean for the worst nights,  
7       worst nights and days?

8       **Q.**     I'm sorry, can you repeat that?

9       **A.**     Do you mean on the worst nights or across the board?

10      **Q.**     Well, as a general matter, do you agree that in  
11      addition to entraining a Non-24 patient, that tasimelteon  
12      can also increase total sleep time per day and reduce  
13      total naptime per day?

14      **A.**     When patients are most symptomatic, I absolutely  
15      agree. I would need to look at the SET/RESET paper to  
16      give you the answer. I don't remember off the top of my  
17      head.

18      **Q.**     All right. Thank you.

19             All right. Let's shift gears a bit to the seven- to  
20      nine-hour sleep period limitation, if we can, and let's go  
21      back to JTX-28. Let's look at the label, and I'd like to  
22      focus on Section 14.1.

23             Let me know when you're there, Doctor.

24      **A.**     Yes.

25             **MR. PICKARD:** If we go to the Table 3,

1 Mr. Brooks. Blow that up a bit.

2 **BY MR. PICKARD:**

3 **Q.** So what we see here are the results of study 1 and  
4 study 2 for Hetlioz, correct?

5 **A.** Yes.

6 **Q.** And for study 1, patients in the Hetlioz group --

7 **MR. PICKARD:** Maybe we can show the text above  
8 the table, Mr. Brooks, the page before this. Sorry. That  
9 last paragraph.

10 **BY MR. PICKARD:**

11 **Q.** See where it says: In study 1, patients in the  
12 Hetlioz group had at baseline an average of 195 minutes of  
13 nighttime sleep?

14 **A.** Yes.

15 **Q.** And 137 minutes of daytime naptime? Did I read that  
16 correctly?

17 **A.** You're missing that it's 25 percent most symptomatic  
18 days and nights, but agreed.

19 **Q.** Okay. Fair point.

20 So they took the worst -- the observation --  
21 25 percent of the observation for the worst nights and  
22 worst days, and those are summarized in Table 3, correct?

23 **A.** Yes.

24 **Q.** And so if the baseline sleep was 195 minutes, we can  
25 agree that's a little more than three hours, right?

~~Combs~~ - Cross

1       **A.**    Yes.

2       **Q.**    And according to study 1 results, patients on average  
3       saw an improvement of 50 minutes on their worst 25 percent  
4       of nights, correct?

5       **A.**    Yes.

6       **Q.**    Which gets you in the neighborhood of four hours.

7       **A.**    Yes.

8       **Q.**    And that's -- of course we can agree that's less than  
9       seven.

10      **A.**    Yes.

11      **Q.**    But for you that's not a problem because the claim  
12      language is not about actual sleep, it is just about  
13      having an opportunity to sleep, right?

14      **A.**    It's about sleep opportunity. And then with this --  
15      this is the worst nights, and so I have certainly slept  
16      four hours on nights I tried to sleep eight.

17      **Q.**    All right. Dr. Combs, if we could go to the '604  
18      patent, JTX-1.

19                   **MR. PICKARD:** And I'd like to put Claim 3 and  
20      Claim 1 up, please.

21                   And if you could highlight, Mr. Brooks, the  
22      phrase -- beginning at: Awakening at or near target wake  
23      time of seven-to-nine hours.

24      **BY MR. PICKARD:**

25      **Q.**    All right. See that claim language, Dr. Combs?

~~Combs~~ - Cross

1       **A.**    Yes.

2       **Q.**    You agree that what that phrase means is that the  
3       patient first sets out a target bedtime and a  
4       corresponding target wake time, which are approximately  
5       seven-to-nine hours apart, right?

6       **A.**    Yes.

7       **Q.**    And you heard Dr. Polymeropoulos testify today that  
8       the label doesn't instruct as to the length of a patient's  
9       sleep period.

10       Did you hear that?

11       **A.**    That was difficult to follow because it seemed like  
12       you were talking about sleep period and he was talking  
13       about total sleep, so...

14       **Q.**    Well, if Dr. Polymeropoulos said that, do you agree  
15       with that?

16       **A.**    That -- sorry. Say that again.

17       **Q.**    That the label does not instruct as to the length of  
18       a patient's sleep period?

19       **A.**    As I discussed, it provides instructions on, like,  
20       the sleep period. Like that's -- it's -- so you take it  
21       at bedtime, one would expect to sleep seven-to-nine hours.  
22       So the seven-to-nine hours is not there. The words are  
23       not there, then I agree.

24       **Q.**    All right. And were you present when  
25       Dr. Polymeropoulos testified that the label does not talk

~~Combs~~ - Cross

1 about being -- there being a target wake time relative to  
2 a target bedtime.

3 Do you agree with that testimony?

4 **A.** I think a target awake time is going to follow  
5 bedtime. So if you know they are separated by  
6 seven-to-nine hours, one follows the other.

7 **Q.** Right. Well, that aside, we can agree that the  
8 labels do not explicitly talk about the seven to nine-hour  
9 sleep window; is that right?

10 **A.** I agree the words are not there.

11 **Q.** All right. Let's shift gears and talk about the  
12 drug-drug interaction patents. I guess for starters, I  
13 want to make sure I understand your opinions for these  
14 patents.

15 And we have the CYP1A2 inhibitor patent, if we will,  
16 and the CYP3A4 inducer, which requires rifampin, right?

17 **A.** Yes.

18 **Q.** And the claims require that you have a patient that's  
19 on one of these relevant drugs, that you discontinue the  
20 treatment and then you administer or prescribe  
21 tasimelteon, right?

22 **A.** Yes.

23 **Q.** So rifampicin, which is claimed by the '910 patent,  
24 that is indicated for some serious conditions including  
25 tuberculosis, right?

1       **A.**    Yes.

2       **Q.**    And if an active case of tuberculosis is left  
3       untreated, it can have some serious health consequences up  
4       to and including death?

5       **A.**    Yes.

6       **Q.**    So is it -- is it your opinion that if a patient  
7       presented, a Non-24 patient, with an active TB case and  
8       they were on a course of rifampicin, that a physician  
9       reading the defendants' label would be instructed to  
10      discontinue rifampicin and put that patient on  
11      tasimelteon?

12      **A.**    It doesn't say anything about stopping it totally.  
13      So I would think that they would let them finish the  
14      course of rifampin. And then when the course is  
15      completed, they would then stop, whether that's in a month  
16      or a couple weeks or whatever, to let them finish their  
17      rifampin, discontinue it once they no longer need it, and  
18      then start tasimelteon.

19      **Q.**    Okay. And so in your understanding of the claims,  
20      allowing the course, for example, rifampicin to  
21      successfully run its course, that's the same as  
22      discontinuing it as it appears in the claims?

23      **A.**    So someone would have to make the decision to  
24      discontinue it.

25      **Q.**    And I don't think you're understanding my question.

1 Are you equating allowing a course of rifampicin to  
2 complete, that is, treat the TB in the case we've been  
3 discussing, is that covered by the word "discontinue" in  
4 the claims of the CYP patents?

5 **A.** So someone would have to decide to stop it. It  
6 wouldn't just magically go away. And so I think that's  
7 where the disagreement is between us.

8 **Q.** All right. You've prescribed Hetlioz to Non-24  
9 patients in your clinical practice?

10 **A.** Yes.

11 **Q.** Have you ever taken a patient off of fluvoxamine --

12 **A.** No.

13 **Q.** -- in order to provide Hetlioz?

14 **A.** No.

15 **Q.** Okay. And fluvoxamine is one of the three -- just so  
16 we are clear, one on the three CYP1A2 inhibitors in the  
17 '829 patent, right?

18 **A.** Yes.

19 **Q.** Ciprofloxacin is another.

20 And so my question is: In your clinical practice,  
21 have you ever taken a patient off of ciprofloxacin and  
22 then prescribed that patient with Hetlioz, a Non-24  
23 patient?

24 **A.** No.

25 **Q.** How about for verapamil? That's another drug covered



1 by the '829 patent, right?

2 **A.** Correct.

3 **Q.** Have you ever, in your clinical practice, taken a  
4 Non-24 patient off of verapamil and put them on Hetlioz?

5 **A.** No.

6 **Q.** And rifampicin, that's the particular inducer that's  
7 covered by the '910 patent, right?

8 **A.** Yes.

9 **Q.** In your clinical practice, you've never taken a  
10 patient off of rifampicin in order to prescribe Hetlioz,  
11 have you?

12 **A.** No.

13 **Q.** In fact, in forming with your opinions in this case  
14 for patent infringement on the '604 patent, you didn't  
15 rely on a single instance where a patient was taken off of  
16 a CYP1A2 inhibitor or a CYP3A4 inducer and then treated  
17 with tasimelteon; isn't that right?

18 **A.** Did I personally do that?

19 **Q.** That anyone did?

20 **A.** No.

21 **Q.** All right. Be that as it may, we can agree the  
22 covered CYP1A2 inhibitors and the CYP3A4 inducer, they do  
23 cover some rather serious conditions.

24 You agree with that?

25 **A.** Yes.

~~Combs~~ - Cross

1 Q. Fluvoxamine, it's indicated for OCD; is that right?

2 A. Yes.

3 Q. And are you aware that the label for fluvoxamine has  
4 warnings concerning the discontinuation of treatment for  
5 fluvoxamine and other similar SSRIs?

6 A. I would need to review it.

7 Q. Okay. You believe the -- actually, if you looked in  
8 your binder to Tab 132, please, DTX- 132.

9 Are you there, Doctor?

10 A. Yes.

11 Q. Do you recognize this as a label for fluvoxamine?

12 A. Yes.

13 Q. Okay. And if you turn to Page 11 of this exhibit --  
14 well, no.

15 MR. PICKARD: I guess at this moment, I'd like  
16 to move for the admission of DTX- 132, Your Honor.

17 MR. KLEIN: No objections.

18 THE COURT: All right. It's admitted.

19 Did you say 132?

20 MR. PICKARD: Yes, DTX- 132.

21 (DTX-132 is admitted into evidence.)

22 BY MR. PICKARD:

23 Q. All right. If you could turn to Page 11 of that  
24 document, Dr. Combs, there's a heading "Discontinuation of  
25 Treatment."

~~Combs~~ - Cross

1 Do you see that?

2 **A.** Yes.

3 **Q.** And you see where it says, "During marketing of  
4 Luvox"?

5 That's fluvoxamine, right?

6 **A.** Yes.

7 **Q.** "Tablets and other SSRIs and SNRIs" -- I'll skip the  
8 parenthetical -- "there have been spontaneous reports of  
9 adverse events occurring upon discontinuation of these  
10 drugs, particularly when abrupt, including the  
11 following" -- and it lists a number of adverse health  
12 events?

13 **A.** Yes.

14 **Q.** Okay.

15 All right. Let's talk about ciprofloxacin. That's  
16 indicated for some serious bacterial infections, including  
17 the plague, right?

18 **A.** I would need to look up the plague. I've never  
19 treated it. I am familiar with it for use of urinary  
20 tract infections, off the top of my head.

21 **Q.** Why don't we go to the DDX- 128.

22 Are you there, Dr. Combs?

23 **A.** Yes.

24 **Q.** Do you recognize DTX- 128 as the label for Cipro?

25 **A.** Yes.

~~Combs~~ - Cross

1 Q. Okay. And if you could turn --

2 MR. PICKARD: Well, Your Honor, at this point,  
3 I move for the admission of DTX- 128, please.

4 MR. KLEIN: No objection.

5 THE COURT: It's admitted.

6 (DTX-128 admitted into evidence.)

7 BY MR. PICKARD:

8 Q. And if you could turn to Page 5, you'll see that's  
9 the second page on -- that's part of the Indications and  
10 Usage section.

11 Do you see that?

12 A. Yes.

13 Q. And if you look at the heading, 1.8, do you see that?

14 A. Yes.

15 Q. And that that shows ciprofloxacin is indicated for  
16 the plague?

17 A. Yes.

18 Q. All right. Let's talk about verapamil.

19 Verapamil, you're aware, that's indicated for  
20 treatment of angina?

21 A. I believe you.

22 Q. Angina is a condition marked by severe pain in the  
23 chest, often -- also spreading to the shoulders, arms and  
24 neck, caused by inadequate blood supply to the heart; is  
25 that right?

**Combs - Redirect**

1       **A.**    Yes.

2       **Q.**    All right.  And we've already talked about TB, which  
3       rifampicin is indicated for.

4               **MR. PICKARD:**  No further questions, Your Honor.

5               **THE COURT:**  All right.  Thank you.

6               Redirect.

7                               REDIRECT EXAMINATION

8       **BY MR. KLEIN:**

9       **Q.**    Dr. Combs, you were asked about Vanda's draft label,  
10       which defendants had marked as DTX- 139.

11              Do you remember that?

12       **A.**    Yes.

13       **Q.**    And have you ever seen it in your practice as a  
14       physician?

15       **A.**    No.

16       **Q.**    You were asked whether you heard Dr. Polymeropoulos'  
17       testimony, correct?

18       **A.**    Yes.

19       **Q.**    And then you were asked whether Vanda submitted the  
20       draft to FDA and FDA rejected it, correct?

21       **A.**    Yes.

22       **Q.**    Do you have any personal knowledge, one way or the  
23       other, whether Vanda submitted to the FDA -- that label to  
24       FDA or that FDA rejected it?

25       **A.**    No.

**Pandrapragada - Direct**

1                   **MR. KLEIN:** No further questions, Your Honor.

2                   **THE COURT:** All right. You may step down.

3 Thank you.

4                   **MR. GROOMBRIDGE:** Your Honor, Vanda's next  
5 witness is Mr. Ravi Pandrapragada. And my colleague,  
6 Ms. Young, will be presenting this witness.

7                   **THE CLERK:** Please state and spell your name  
8 for the record.

9                   **THE WITNESS:** Ravi Pandrapragada.

10                  Ravi Pandrapragada, having been called as a witness,  
11 having affirmed or duly sworn under oath, testified as  
12 follows:

13                                   DIRECT EXAMINATION

14                  **BY MS. YOUNG:**

15                  **Q.** Josephine Young for Vanda. Good afternoon,  
16 Mr. Pandrapragada.

17                  Would you please introduce yourself to the Court.

18                  **THE COURT:** You might want to get closer to the  
19 microphone.

20                  **MS. YOUNG:** Is that better?

21                  Is this better?

22                  **THE COURT:** We're having technical problems, so  
23 go like this in the microphone.

24                  **MS. YOUNG:** I'll just --

25                  **THE COURT:** Project.

**MS. YOUNG:** Okay.

BY MS. YOUNG:

Q. Good afternoon, Mr. Pandrapragada. Would you please introduce yourself to the Court.

**A.** Yes. Good afternoon. My name is Ravi Pandrapragada. I am a pharmaceutical scientist. I have been a pharmaceutical scientist. I've been employed at Vanda for almost 11 years.

**THE COURT:** Can you repeat that? Employed  
what?

**THE WITNESS:** With Vanda Pharmaceuticals for about 11 years.

**THE COURT:** Okay. If I could just ask if you could please speak slowly.

**THE WITNESS:** Sure.

**THE COURT:** Thank you.

**THE WITNESS:** Sorry.

**THE COURT:** That's all right. It's just very difficult sometimes.

BY MS. YOUNG:

**Q.** What is your title at Vanda?

**A.** I'm an associate director of CMC.

**Q.** What does CMC stand for?

**A.** Chemistry, manufacturing and controls.

**Q.** What does the CMC division do?

**Pandrapragada - Direct**

1     **A.**    In the pharmaceutical industry, the manufacturing,  
2     science and quality control activities that are related to  
3     those are usually referred to as CMC.

4     **Q.**    If you could turn to the first tab in your binder,  
5     which should be labeled PTX- 828.

6           Do you recognize this document?

7     **A.**    Yes.

8     **Q.**    What is it?

9     **A.**    This is my CV.

10    **Q.**    Did you prepare this CV?

11    **A.**    Yes.

12    **Q.**    Was your CV accurate?

13    **A.**    Yes.

14           **MS. YOUNG:**  I'd like to offer PTX- 828 into  
15    evidence.

16           **MS. WELLS:**  No objection.

17           **THE COURT:**  All right.  It's admitted.

18           (PTX-828 admitted into evidence.)

19    **BY MS. YOUNG:**

20    **Q.**    Mr. Pandrapragada, what is your educational  
21    background?

22    **A.**    I have two master's degrees.  One in organic  
23    chemistry from Osmania University in India, and University  
24    of Missouri-Columbia, second master's degree in chemistry.

25    **Q.**    When did you obtain your master's degree?



**Pandrapragada - Direct**

1     **A.**    My first master's degree I obtained in 1998. And my  
2     second master's degree was in 2006.

3     **Q.**    Since obtaining your first master's degree, have you  
4     worked in the pharmaceutical industry?

5     **A.**    Yes, I have.

6     **Q.**    Did any of that work involve analytic advising of  
7     pharmaceutical compounds for impurities?

8     **A.**    Yes.

9     **Q.**    How about designing and developing analytical methods  
10    for detecting impurities?

11    **A.**    Yes, many of them.

12    **Q.**    Now, let's turn to the patent at issue here. Could  
13    you turn to the next tab in your binder, which should be  
14    labeled JTX- 006?

15    **A.**    Yes.

16    **Q.**    Do you recognize this document?

17    **A.**    Yes.

18    **Q.**    What is it?

19    **A.**    This is the '465 patent for highly purified  
20    pharmaceutical grade tasimelteon.

21           (Reporter clarification.)

22           **THE WITNESS:** This is the '465 patent highly  
23    purified pharmaceutical grade tasimelteon.

24    **BY MS. YOUNG:**

25    **Q.**    Are you an inventor on the '465 patent?

**Pandrapragada - Direct**

1       **A.**     Yes.

2       **Q.**     Who are the other inventors of the patent?

3       **A.**     Dr. Deepak Phadke and Natalie Platt.

4       **Q.**     Who are they?

5       **A.**     Dr. Phadke is our head of CMC. And Natalie Platt was  
6 my colleague in CMC.

7               **MS. YOUNG:** I would like to offer JTX- 006 into  
8 evidence.

9               **MS. WELLS:** No objection, Your Honor.

10              **THE COURT:** It's admitted.

11              (JTX-006 is admitted into evidence.)

12       **BY MS. YOUNG:**

13       **Q.**     Let's talk about tasimelteon.

14              Did Vanda itself invent the compound tasimelteon?

15       **A.**     No, it was BMS.

16       **Q.**     Was there a point when Vanda acquired tasimelteon  
17 from BMS?

18       **A.**     I believe it was in 2004 when license for BMS -- from  
19 BMS.

20       **Q.**     When did you start work on the tasimelteon project?

21       **A.**     I started working on tasimelteon in summer of 2010.  
22 That's when I joined Vanda.

23       **Q.**     As part of your work on the tasimelteon project, did  
24 you review any documents to familiarize yourself with the  
25 manufacturing process for tasimelteon as it had existed

**Pandrapragada - Direct**

1 before you started?

2 **A.** Yes. I had reviewed manufacturing process documents  
3 and clinicals for all the work that has been done on  
4 tasimelteon prior to me joining Vanda.

5 **Q.** Did that include BMS documents?

6 **A.** Yes.

7 **Q.** At a very high level, what is your understanding of  
8 what stage of development BMS's manufacturing process was  
9 at when it sold the product to Vanda?

10 **A.** The BMS process, it was pretty early stages of the  
11 development. They had a process for manufacturing  
12 tasimelteon. The process was not clean. There were much  
13 optimization needed to be done. The quality of the  
14 product was not that great. There were many impurities  
15 that were present in the tasimelteon. Lot more work  
16 needed to be done in order for -- to bring the -- for  
17 commercially manufacturing and scalable.

18 **Q.** What is your understanding of how much work BMS had  
19 done regarding the impurities when they sold the franchise  
20 to Vanda?

21 **A.** The initial BMS logs that I have reviewed had many  
22 impurities. It was not of that great quality. There's  
23 not much information that I obtained from BMS.

24 **Q.** Mr. Pandrapragada, let's look at some of those  
25 documents that Vanda inherited from BMS.

**Pandrapragada - Direct**

1 Can you turn in your binder to the next tab, which  
2 would be DTX- 66.

3 **A.** Yes.

4 **Q.** Do you recognize this document?

5 **A.** Yes.

6 **Q.** What is this document?

7 **A.** This is BMS's investigation of new drug application,  
8 CMC sections.

9 **Q.** Is this one of the documents you reviewed as part of  
10 your work on tasimelteon at Vanda?

11 **A.** Yes, I have.

12 **MS. YOUNG:** I'd like to offer DTX- 66 into  
13 evidence.

14 **MS. WELLS:** No objection.

15 **THE COURT:** It's admitted.

16 (DTX-66 is admitted into evidence.)

17 **MS. YOUNG:** Mr. Weir, can you put DTX- 66 up on  
18 the screen and turn to Page 50, please.

19 **BY MS. YOUNG:**

20 **Q.** Mr. Pandrapragada, what is on Page 50 of DTX- 66?

21 **A.** These are the specifications for BMS tasimelteon drug  
22 substance.

23 **Q.** And what is a specification?

24 **A.** A specification is quality attributes and the limits  
25 for those quality attributes in the drug.

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1     **Q.**   And do you see, about five lines from the bottom,  
2     there's --

3             Thank you, Mr. Weir.

4             -- do you see an entry called "Impurity Content  
5     HPLC"?

6     **A.**   Yes.

7     **Q.**   What is HPLC?

8     **A.**   HPLC is a technique of pharmaceutical industries  
9     commonly used to measure the purity and the contents of  
10    impurities in a given drug.

11    **Q.**   And do you see at the top of the specification, it  
12    has "Specifications: Min/Max"?

13    **A.**   Yes.

14    **Q.**   And then under the "Impurity Content for Individual,"  
15    it has 1?

16    **A.**   Yes.

17    **Q.**   And for "Total" it has 3?

18    **A.**   Yes.

19    **Q.**   What does that mean?

20    **A.**   That means that the drug can have up to 1 percent of  
21    any given individual impurity. And for total impurities,  
22    the drug can have up to 3 percent of impurities present in  
23    the drug.

24    **Q.**   What is the significance of having an impurity limit  
25    of 1 percent for an individual impurity with 3 percent for

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1 total impurities?

2 **A.** A 1 percent limit for any individual impurity is  
3 considered very high. And 3 percent total impurities is  
4 also considered very high and the drug is not clean.

5 **Q.** And if we can turn to Page 54 and 55 of this  
6 document.

7 **MS. YOUNG:** And, Mr. Weir, if you can put those  
8 two pages side by side and focus it on the table there.

9 **BY MS. YOUNG:**

10 **Q.** Mr. Pandrapragada, what is this table?

11 **A.** This table actually is a coalition of all the  
12 impurities that are presented in several BMS batches.

13 **Q.** How many impurities are being shown here?

14 **A.** There are about 12 impurities that are reported here.

15 **Q.** How are those impurities labeled?

16 **A.** They are labeled as a nonimpurities with their  
17 related retention times.

18 **Q.** Are any of these 12 impurities identified by  
19 structure?

20 **A.** No.

21 **Q.** And I believe you mentioned relative retention time.

22 What is relative retention time?

23 **A.** Relative retention time, when you actually introduce  
24 your drug sample with impurities into the HPLC system that  
25 you analyze, the retention time, the time that the drug

1 retains is called retention time when it comes out of the  
2 column, HPLC column.

3 And the -- all other components, the retention time  
4 components later to remain peak of the drug is called  
5 relative retention time.

6 The components that come out earlier than the main  
7 drug usually will have a retention time of less than one.  
8 And the components that come out of the system after the  
9 drug, will have a relative retention time of more than  
10 one.

11 **Q.** Is relative retention time some kind of abbreviated  
12 RRT?

13 **A.** Yes.

14 **Q.** Is it common for the industry to refer to impurities  
15 by RRT?

16 **A.** For unknown impurities, yes.

17 **Q.** Why?

18 **A.** Because when a HPLC method is -- remains same, when  
19 you inject the relative retention time of a particular  
20 impurity, will remain the same. And for impurities that  
21 are specifically not known, are usually labeled with  
22 relative retention times.

23 **Q.** Would you refer to a compound that has been  
24 identified by structure by its RRT?

25 **A.** No. For known impurities, usually they are

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1 identified with their names.

2 **Q.** Now, looking back at the table on the DTX- 66 here,  
3 what is being shown in each of the rows of the table?

4 **A.** Each row has the content of the impurities that are  
5 present in BMS batches.

6 **Q.** And what is shown in each of the columns?

7 **A.** Each of the columns, the amount of the impurities for  
8 particular RRT impurity.

9 **Q.** Do you recall if any of these batches were intended  
10 for clinical use?

11 **A.** The last batch, the last row, C026A, was used in the  
12 initial clinical study.

13 **Q.** And do you see in the last column, it has "Total  
14 Impurity Content"?

15 **A.** Yes.

16 **Q.** What does that refer to?

17 **A.** That is amount of all the impurities that are present  
18 in the drug substance.

19 **Q.** Is it limited to the impurities that are listed by  
20 RRT?

21 **A.** Yes. May or may not be. There might be some other  
22 impurities that may be present for which are not reported  
23 in this table. The total presents the -- all of the  
24 impurities that come out of the system.

25 **Q.** And how many total impurities are reported for this



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1 clinical batch C026A?

2 **A.** There are ten impurities that are reported here.

3 **Q.** I'm sorry. And what is the total impurity content  
4 for that batch?

5 **A.** It's 1.89 percent.

6 **Q.** In your review of the materials that Vanda acquired  
7 on the BMS, did you learn what FDA did in response to the  
8 submission by BMS?

9 **A.** The initial response was BMS clinical study on hold  
10 because the batch that they were planning to use in the  
11 clinical study was not clean.

12 **Q.** Let's talk about that a little more. If you could  
13 turn to your binder to the next document, which is  
14 DTX- 48.

15 Do you recognize this document?

16 **A.** Yes. This is the documentation of communication  
17 between BMS and the FDA regarding the clinical report.

18 **Q.** Is this one on the documents you reviewed as part of  
19 your work on tasimelteon at Vanda?

20 **A.** Yes. I have seen this document.

21 **MS. YOUNG:** I'd like to offer DTX- 48 into  
22 evidence.

23 **MS. WELLS:** No objection.

24 **THE COURT:** It's admitted.

25 (DTX-48 is admitted into evidence.)

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**BY MS. YOUNG:**

**Q.** Mr. Pandrapragada, can you turn to Page 18 of this document?

**MS. YOUNG:** And, Mr. Weir, can you put that up on screen and focus on the second paragraph, please?

**BY MS. YOUNG:**

**Q.** What is -- Mr. Pandrapragada, what was your understanding of BMS's response to FDA's clinical hold?

**A.** Well, I think BMS has told the FDA the impurity levels that are present in the 0C026A lot are not of concern, and they considered these impurity levels of concern qualified.

**Q.** What does qualified impurity mean?

**A.** Qualified impurity means any given impurity in toxicology studies. If there was no known adverse affect found, then those impurities are considered as qualified at that particular level.

**Q.** What is your understanding of whether or not BMS made any changes to the purity of its C026A batch in response to the clinical hold?

**A.** It was not purified. There was no change to the batch that they were planning to use in the clinical study.

**Q.** And do you recall how FDA responded after it received this letter from BMS?

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1     **A.**    I think FDA has agreed with BMS's approach and lifted  
2     the clinical hold.

3     **Q.**    What kind of clinical trial was BMS seeking to  
4     conduct with that clinical batch?

5     **A.**    I believe it's a single-dose study in humans.

6     **Q.**    All right. So now let's turn to Vanda's work.

7            At a very high level after Vanda got tasimelteon from  
8     BMS in 2004, what did you understand Vanda had to do?

9     **A.**    Based on my review of the documents prior to when I  
10    joined Vanda and of the work that I performed after I  
11    joined Vanda, the process was not very well established.

12           Vanda has worked on optimizing the process. They  
13    have identified a new route for the cyclo combinations to  
14    take and we have identified many impurities and we  
15    developed analytical methods and also, we set the limits  
16    for potentially genotoxic tasimelteon impurities, which  
17    were not present in the BMS specifications.

18           And we also identified some new impurities based off  
19    of process and we set specifications for those impurities  
20    as well.

21    **Q.**    So let's start with the analytical methods.

22           In reviewing the materials that Vanda received from  
23    BMS, did you learn what conditions BMS used in its HPLC  
24    analysis for impurities?

25    **A.**    Yes, I have.

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1       **Q.**     And did Vanda make any changes to those conditions?

2       **A.**     As far as I remember, I think we had changed the  
3       solvent composition for the phase. And also we improved  
4       the sensitivity of the method by increasing the  
5       concentration of the sample that is introduced into the  
6       HPLC system.

7       **Q.**     So let's take a look at the document on that. If you  
8       could turn to PTX- 217, which would be the next tab in  
9       your binder.

10      **A.**     Yes.

11      **Q.**     What is this document?

12      **A.**     This is actually an e-mail communication followed by  
13      our analytical procedures section we submitted to the FDA.

14      **Q.**     Is it fair to say that these are part of the NDA?

15      **A.**     NDA submission documents, yes.

16      **Q.**     Are these NDA submission documents documents you  
17      drafted or reviewed as part of your work on tasimelteon at  
18      Vanda?

19      **A.**     Yes, I have.

20               **MS. YOUNG:** I'd like to offer PTX- 217 into  
21      evidence.

22               **MS. WELLS:** No objection.

23               **THE COURT:** It's admitted.

24               (PTX-217 is admitted into evidence.)

25

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1 **BY MS. YOUNG:**

2 **Q.** Mr. Pandrapragada, can you turn to Page 92.

3 **MS. YOUNG:** And, Mr. Weir, if you could blow  
4 that up and focus in on the section on the bottom,  
5 starting on -- talking about impurities by HPLC.

6 **BY MS. YOUNG:**

7 **Q.** Mr. Pandrapragada, what did Vanda tell FDA regarding  
8 the changes it made by BMS's HPLC conditions for  
9 impurities?

10 **A.** I think we mention here the solvent system is changed  
11 from 40, 60 water, and we also increase the concentration  
12 of the sample from 0.4 milligrams for MM2, 1.2 milligrams  
13 to increase the sensitivity of the method.

14 **Q.** And what does it mean to increase the sensitivity of  
15 the method?

16 **A.** When you conclude the sensitivity of the method, you  
17 would be able to see if there are impurities that have low  
18 response that may be undetected at lower concentration,  
19 can be detected with higher concentrations.

20 **Q.** Let's turn very briefly now to Vanda's manufacturing  
21 process. Can you turn to the next tab in your binder.  
22 Actually, two tabs down, PTX-818.

23 **A.** Yes.

24 **Q.** What is this document?

25 **A.** This is Vanda's NDA section, manufacturing process

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1 development, which gives the chronological order of the  
2 manufacturing process development for tasimelteon drug  
3 substance.

4 **Q.** Is this document a document that you drafted or  
5 reviewed as part of your work on tasimelteon at Vanda?

6 **A.** Yes.

7 **MS. YOUNG:** I'd like to offer PTX-818 into  
8 evidence.

9 **MS. WELLS:** No objection.

10 **THE COURT:** It's admitted.

11 (PTX-818 admitted into evidence.)

12 **MS. YOUNG:** If you could focus -- Mr. Weir, if  
13 you could put that on the screen and focus on the third  
14 paragraph.

15 **BY MS. YOUNG:**

16 **Q.** What is the purpose of this section of the NDA?

17 **A.** The purpose of this section is to provide the FDA how  
18 we evolved with our manufacturing process is concerned  
19 since the inception of the initial IND to our NDA  
20 submission and the chronological and historical  
21 information about the process.

22 **Q.** I see a reference to Formosa Laboratory Inc. there.

23 **A.** Yes.

24 **Q.** What is Formosa?

25 **A.** Formosa is a contract manufacturing company who does

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1 work for Vanda.

2 **Q.** How many different processes were finalized enough  
3 for Vanda to present them to FDA?

4 **A.** I believe there are about eight processes.

5 **Q.** Were those processes implemented serially or was  
6 there an overlap in these processes?

7 **A.** There is no overlap. They are implemented  
8 sequentially. Process 1 -- process 2 actually supercedes  
9 process 1, and process 3 supersedes process 2 and so on.

10 **Q.** Which of the eight processes that were disclosed to  
11 FDA were developed by BMS and which were developed by  
12 Vanda?

13 **A.** I believe process 1, 2, 3 are by BMS, and process 4  
14 onwards to process 8 are by Vanda.

15 **MS. YOUNG:** Mr. Weir, if you could turn to  
16 Page 5 of this document.

17 **THE WITNESS:** Yes.

18 **BY MS. YOUNG:**

19 **Q.** What is shown on this page?

20 **A.** This is the current manufacturing process of the  
21 tasimelteon drug substance.

22 **Q.** And did you help prepare a demonstrative with Vanda's  
23 current manufacturing process for tasimelteon?

24 **A.** Yes.

25 **Q.** Let's take a look at that.

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1                   **MS. YOUNG:** Mr. Weir, if you can pull up PTX-5,  
2                   Slide 2.

3                   **BY MS. YOUNG:**

4                   **Q.** Is this the current manufacturing process for  
5                   tasimelteon?

6                   **A.** Yes, it is.

7                   **Q.** Is this tasimelteon on the bottom right?

8                   **A.** Yes.

9                   **Q.** And we're going to focus on the last two steps in  
10                  Vanda's synthesis of tasimelteon.

11                  What kind of compound is the compound labeled  
12                  intermediate 4 at stage 10?

13                  **A.** Intermediate 4 is actually a carboxamide.

14                  **Q.** Can we call that a carboxamide?

15                  **A.** Yes.

16                  **Q.** And what kind of compound is a compound labeled  
17                  intermediate 5 at stage 11?

18                  **A.** It is a methanamine.

19                  **Q.** Can we call that methanamine?

20                  **A.** Yes.

21                  **Q.** In Vanda's manufacturing process for tasimelteon,  
22                  what type of reaction is the step from the carboxamide to  
23                  the methanamine?

24                  **A.** That's actually a reduction step from carboxamide to  
25                  methanamine.



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1 Q. And what type of reaction is the step from the  
2 methanamine to tasimelteon?

3 A. That is step is propionylation.

4 Q. Did BMS's process also contain a reducing step and a  
5 propionylating step?

6 A. Yes, it is.

7 Q. Did Vanda make any improvements to the reducing or  
8 propionylating steps?

9 A. I think -- as well as I remember, there are some  
10 process changes that were made from carboxamide to  
11 tasimelteon for the reduction step. The reason, isn't  
12 changed to lithium aluminum hydride. And also the  
13 quenching step was done using sodium sulfate instead of  
14 methanol that was used by BMS to eliminate the aluminum  
15 salts that may form during the reduction step.

16 And also we introduced additional reprocessing steps  
17 for tasimelteon final drug substance to ensure the quality  
18 of the drug substance is met, and we also introduced  
19 specifications for propionylating agents of the final  
20 reaction would not result in many impurities.

21 Q. So let's talk about that a little bit more.

22 **THE COURT:** Can we have a sidebar.

23 - - -

24 (Whereupon, the following discussion is held at  
25 sidebar.)

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1           **THE COURT:** I'm sure. I am missing something  
2           very, very obvious.

3           So why are we spending all this time on how  
4           Vanda makes its product when you are trying to prove  
5           infringement of drugs made by other companies?

6           **MS. YOUNG:** This is really talking about the  
7           development to get to the '465 patent, why Vanda basically  
8           isolated these impurities and decided to control for them,  
9           what it meant for their process.

10          **MR. STONE:** This is going to play into their  
11          invalidity case. It is not going to play into the  
12          inventor -- we are telling the inventor's story because  
13          during our infringement case, that's in our case-in-chief.  
14          This is -- we learned during this examination that they  
15          are not disputing infringement.

16          Our next witness is our infringement expert.  
17          We learned they are not disputing infringement of many of  
18          the elements of this claim. We narrowed down to what is  
19          being disputed. We are currently reducing the direct of  
20          our infringement expert to be about what's at issue. This  
21          will come back on validity.

22          **THE COURT:** Okay. Ms. Wells, do you want to  
23          say anything? You are welcome to.

24          **MS. WELLS:** No.

25          **MR. ROZENDAAL:** I don't know what it's relevant

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1 to. It seems like a lot of time on stuff that won't  
2 matter at the end of the day. It's their case.

3 **MR. STONE:** If they are no longer asserting  
4 inventorship, whether BMS invented this or not. Part of  
5 their argument is that BMS invented this, and that Vanda  
6 didn't demonstrate that Vanda did the work that led to the  
7 invention is directly responsive to that allegation.

8 **THE COURT:** It's solely going to validity.

9 **MR. STONE:** Yes.

10 **THE COURT:** All right. Anything else?

11 **MR. ROZENDAAL:** No, Your Honor.

12 **MR. GROOMBRIDGE:** Your Honor, taking the  
13 Court's direction, we did have a discussion that we could  
14 stipulate, I think, to some of the elements for this  
15 patent. And so in view of the hour of the day, we were  
16 trying to think when it will get done. Here, we can fill  
17 up the space and work on that overnight and shortcuts.

18 **THE COURT:** I think I will require you to have  
19 to meet. Are you doing infringement then?

20 **MR. GROOMBRIDGE:** The only remaining witness is  
21 our expert on this patent, and what we would be doing is  
22 reducing -- cutting a lot out from what he's saying. It's  
23 no longer contested.

24 **THE COURT:** Okay.

25 **MR. GROOMBRIDGE:** For example, we could play

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1 about 10 minutes of video, if there's any time left and  
2 then wrap up, or we haven't, obviously, seen the cross. I  
3 don't know how long it will be, but it seems like given  
4 the hour, it may make sense, we can wrap up for the day  
5 and try and shortcut what would be coming up next.

6 **THE COURT:** Okay. You've also each heard your  
7 respective openings. I think you need to confer this  
8 evening and decide what do you really need to contest  
9 versus what can you dispense with.

10 **MR. GROOMBRIDGE:** Yes.

11 **THE COURT:** So make sure you do that this  
12 evening.

13 All right. Thank you.

14 (Whereupon, the discussion at sidebar concludes.)

15 - - -

16 **THE COURT:** Go ahead.

17 **BY MS. YOUNG:**

18 **Q.** I believe we were going to start talking about  
19 Impurities 1 through 3, 5 and 6.

20 At the time that Vanda got the tasimelteon franchise  
21 from BMS, for which of Impurities 1 through 3, 5 and 6 had  
22 BMS determined the chemical structure?

23 **A.** None of them.

24 **Q.** Did Vanda set out to determine the structure of  
25 Impurities 1 through 3, 5, and 6?

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1       **A.**    Yes.

2       **Q.**    Why did Vanda do that?

3       **A.**    Because it's important to understand the structures  
4       of the impurities that are presented in the drug  
5       substance. So they are to make sure the -- these  
6       impurities are not of any toxicological concerns. And it  
7       also gives us the opportunity to look at our process and  
8       understand it better so we can introduce proper process  
9       controls so that we can provide information of these  
10      impurities onto Vanda.

11      **Q.**    Did FDA require Vanda to determine the structure of  
12      these impurities?

13      **A.**    No.

14      **Q.**    Did Vanda succeed in identifying the structures of  
15      these impurities?

16      **A.**    Yes.

17      **Q.**    Let's talk about sequence.

18             Did Vanda identify Impurities 1, 2, 3, 5, and 6  
19      around the same time?

20      **A.**    No. They were identified at different times.

21      **Q.**    Which ones were identified first?

22      **A.**    I think Impurity 1, 2, and 3 were identified  
23      initially and later, Impurity 5 and Impurity 6.

24      **Q.**    So let's start with Impurities 1, 2, and 3.

25             When did Vanda realize that what we now call

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1 Impurities 1, 2, and 3 were being formed in the  
2 manufacturing process?

3 **A.** From the documents that I reviewed, I think there  
4 were some batches in 2007, 2008 campaign. We found  
5 these -- Vanda found these impurities in these batches and  
6 at that time, Vanda decided to identify these impurities.

7 **Q.** Was there anything in the materials that you received  
8 from BMS that could help you determine the structures of  
9 Impurities 1, 2, or 3?

10 **A.** No.

11 **Q.** Did Vanda attempt to determine the structure of those  
12 impurities?

13 **A.** Can you repeat the question?

14 **Q.** Sure.

15 Did Vanda attempt to identify the structures of these  
16 impurities?

17 **A.** Yes.

18 **Q.** How quickly was Vanda able to determine those  
19 structures?

20 **A.** It took some time for us, a few years, to completely  
21 determine the structures of these impurities.

22 **Q.** If you could turn to the next tab in your binder,  
23 which would be PTX-819, do you recognize this document?

24 **A.** Yes.

25 **Q.** What is this document?

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1     **A.**     This document is the impurity identification report  
2     for RRT 1.26 and RRT 1.53, which we call Impurity 1 and  
3     Impurity 3.

4     **Q.**     Is this one of the documents you reviewed as part of  
5     your work on tasimelteon and Vanda?

6     **A.**     Yes.

7                 **MS. YOUNG:**   I'd like to offer PTX-819 into  
8     evidence.

9                 **MS. WELLS:**   No objection.

10                **THE COURT:**   It's admitted.

11                         (PTX-819 admitted into evidence.)

12                **MS. YOUNG:**   Mr. Weir, if you could put PTX-819  
13     up on the screen, please.

14     **BY MS. YOUNG:**

15     **Q.**     What is the date of this report?

16     **A.**     April 2008.

17     **Q.**     And I see Shasun there.   What is Shasun?

18     **A.**     Shasun is a contract manufacturer that does work for  
19     Vanda.

20     **Q.**     Now let's turn to Page 24 of this document.

21                **MS. YOUNG:**   Mr. Weir, if we could just blow up  
22     the first section, Tentative Structures for RRT 1.26.

23     **BY MS. YOUNG:**

24     **Q.**     Mr. Pandrapragada, what is being shown here with  
25     regard to impurity at RRT 1.26?

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1     **A.**   Well, based on the initial LCMS3, there were three  
2     possible structures that were proposed for RRT 1.26  
3     impurity.

4     **Q.**   At this time in 2008, did Vanda know which structures  
5     were the correct structures for impurity at RRT 1.26?

6     **A.**   No, we had to do further work to confirm and identify  
7     which impurity.

8                 **MS. YOUNG:**   And Mr. Weir, if you could now  
9     focus on the next section, which is the impurity at RRT  
10    1.53.

11   **BY MS. YOUNG:**

12   **Q.**   At this time in 2008, had Vanda confirmed the  
13    structure for an impurity at RRT 1.53?

14   **A.**   Its structure was assigned, but further work needed  
15    to be done to familiarize and identify this impurity.

16   **Q.**   What more needed to be done to figure out the correct  
17    structure for these impurities?

18   **A.**   I think the approach Vanda took is synthesized all  
19    three structures that were identified for 1.26 RRT. And  
20    also we synthesized the 1.53 RRT structure, and then we  
21    spiked those impurities into the drug to confirm retention  
22    time of those synthesized impurities. And then we  
23    determined the structure confirmation for the impurities.

24   **Q.**   Were you involved in that work?

25   **A.**   Yes, I have.



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1     **Q.**   And after that work, was Vanda able to figure out the  
2     structure for the impurity at RRT 1.26?

3     **A.**   Yes.

4                 **MS. YOUNG:**   Mr. Weir, if we can go back up to  
5     that section about RRT 1.26.

6     **BY MS. YOUNG:**

7     **Q.**   What is the current structure for the impurity at RRT  
8     1.26?

9     **A.**   The current structure is Structure 2.

10    **Q.**   And what is that impurity now called?

11    **A.**   Impurity 1.

12    **Q.**   What about that first compound structure 1? Is that  
13    also in an impurity in Vanda's manufacturing process?

14    **A.**   Yes, it is presented as an impurity but not RRT 1.26.  
15    That compound comes at RRT1.29 which is now called  
16    Impurity 2.

17    **Q.**   And what about the third compound, structure 3, is  
18    that an impurity found in Vanda's manufacturing process?

19    **A.**   We did not find this compound in any of the Vanda's  
20    lots.

21                 **MS. YOUNG:**   And now let's look at, Mr. Weir, if  
22    we could, RRT 1.53.

23    **BY MS. YOUNG:**

24    **Q.**   Is this impurity found in Vanda's manufacturing  
25    process?

**Pandrapragada - Direct**

1       **A.**    Yes.

2       **Q.**    And what is this impurity now called?

3       **A.**    This impurity is now called Impurity 3.

4       **Q.**    When did Vanda confirm the actual structure of  
5       Impurities 1, 2, and 3?

6       **A.**    It was sometime in late 2011.

7       **Q.**    Was it useful to Vanda to know the structures of  
8       Impurities 1, 2, and 3?

9       **A.**    Yes, it was very useful because of -- based off these  
10       structures, we were able to identify the source of the  
11       formation of these impurities.

12       **Q.**    Let's turn to that.

13               Did you help prepare a demonstrative that helped  
14       explain how Impurities 1 through 3 might be formed?

15       **A.**    Yes.

16               **MS. YOUNG:**   Can we put up PDX-5, Slide 3.

17       **BY MS. YOUNG:**

18       **Q.**    What is shown at the top here?

19       **A.**    The top potential impurities that may be present in  
20       the final synthesis step, the reagent that is used for  
21       propionylating.

22       **Q.**    And how is Impurity 1 formed?

23       **A.**    Impurity 1 is formed with the reaction of the final  
24       intermediate with one of the impurities that may be  
25       present in the propionylating agent named as isovaleric

1 chloride and it forms Impurity 1.

2 **Q.** What about Impurities 2 and 3, if you can see the  
3 next slide?

4 **A.** Impurity 2 and 3 are also formed by the reaction of  
5 the final intermediate with the impurities that might be  
6 present in the propionylating agent, namely methanamine  
7 fluvoxamine.

8 **Q.** Now let's turn our attention to Impurities 5 and 6.

9 When did Vanda first observe what we now know are  
10 Impurities 5 and 6?

11 **A.** I think in second half of 2012 we formed these two  
12 impurities in some of our stability lots, and we decided  
13 to identify and look at what is in these impurities.

14 **Q.** Were you involved in the work to identify these  
15 structures?

16 **A.** Yes.

17 **Q.** Did you decide to synthesize these impurities to  
18 determine these structures?

19 **A.** Yeah. We attempted to synthesize these impurities,  
20 but because of the complex nature of these compounds, we  
21 were not successful in synthesizing these impurities.  
22 Instead, we isolated these impurities by taking the drug  
23 that has these impurities and using the propionylating  
24 HPLC technique, we isolated these impurities from the drug  
25 and then fully categorized.

**Pandrapragada - Direct**

1       **Q.** Was there anything in the materials that you received  
2       from BMS that could help you determine the structures of  
3       Impurities 5 or 6?

4       **A.** No, nothing.

5       **Q.** If you can turn to the next tab in your binder, which  
6       is PTX-820.

7             Do you recognize this document?

8       **A.** Yes.

9       **Q.** What is this document?

10       **A.** This is the identification that was conducted for  
11       identifying eight impurities in tasimelteon.

12       **Q.** Is this a document that you reviewed as part of your  
13       work on tasimelteon at Vanda?

14       **A.** Yes.

15             **MS. YOUNG:** I'd like to offer PTX-820 into  
16       evidence.

17             **SPEAKER:** No objection.

18             **THE COURT:** All right. It's admitted.

19             (PTX-820 admitted into evidence.)

20             **MS. YOUNG:** Mr. Weir, if you could put that up  
21       on the screen. Thank you.

22       **BY MS. YOUNG:**

23       **Q.** This document mentions Sai. Who is Sai?

24       **A.** Sai is a contractor manufacturer for Vanda.

25       **Q.** You've mentioned contract manufacturers a few times

**Pandrapragada - Direct**

1 now. Does Vanda work with contract manufacturers often?

2 **A.** Yes.

3 **Q.** Why is that?

4 **A.** Vanda do not have a manufacturing facilities so we  
5 outsource this work to our contractor manufacturers.

6 **Q.** All right.

7 **MS. YOUNG:** Mr. Weir, if you could turn to  
8 Page 7, please.

9 **BY MS. YOUNG:**

10 **Q.** At a high level, what is being disclosed on Page 7,  
11 Mr. Pandrapragada?

12 **A.** Page 7 talks about the process for isolation and how  
13 we categorized the impurity at RTT 1.548.

14 **Q.** And what is that impurity now called?

15 **A.** This impurity is now called Impurity 5.

16 **Q.** And if you could turn to Page 14.

17 At a very high level, what is being disclosed with  
18 regard to the -- what is being disclosed here?

19 **A.** This, again, talks about the isolation and  
20 categorization of impurity that is present at RRT 1.57.

21 **Q.** And what is that impurity now called?

22 **A.** That impurity is now called Impurity 6.

23 **Q.** Was Vanda able to determine the structures of  
24 Impurity 5 and 6?

25 **A.** Yes.

**Pandrapragada - Direct**

1       **Q.**     Was that useful to Vanda to know those structures?

2       **A.**     Yes, it was useful to make sure that these impurities  
3       are not of any safety concern. And also we were able to  
4       control these impurities and specifications in our NDA to  
5       control these impurities.

6       **Q.**     Does Vanda have any safety concerns about Impurities  
7       1 through 3, 5 and 6?

8       **A.**     Based on the structures, there were no flags.

9       **Q.**     Would you have been able to make that determination  
10      if Vanda had not identified structures of the Impurities 1  
11      through 3, 5 and 6?

12      **A.**     No.

13      **Q.**     How long did it take Vanda to do this work?

14      **A.**     It took several years of work.

15      **Q.**     We've been referring to these impurities with the  
16      names Impurities 1, 2, 3, 5, and 6. Did you help prepare  
17      a demonstrative with these structures?

18      **A.**     Yes.

19               **MS. YOUNG:** If we could put up PDX-05, Slide 5.

20      **BY MS. YOUNG:**

21      **Q.**     Does Vanda refer to these impurities as Impurities 1,  
22      2, 3, 5 and 6 in its regulatory filings to FDA for  
23      tasimelteon?

24      **A.**     Yes, that is correct.

25      **Q.**     Including Vanda's NDA?

**Pandrapragada - Cross**

1       **A.**     Yes.

2       **Q.**     And are they impurities called Impurities 1, 2, 3, 5,  
3       and 6 in the '465 patent?

4       **A.**     Yes.

5               **MS. YOUNG:**   I have no further questions.

6               **THE COURT:**   All right.   Thank you.

7               Cross-examination, Ms. Wells.

8               **MS. WELLS:**   May we approach with binders?

9               Hello, Dr. Pandrapragada.   Nice to see you  
10       again.

11              **THE WITNESS:**   Nice to see you again.

12                               CROSS-EXAMINATION

13       **BY MS. WELLS:**

14       **Q.**     Dr. Pandrapragada, you are familiar with the ICH  
15       Guideline, correct?

16       **A.**     Yes.

17       **Q.**     And the ICH Guideline is actually the standard for  
18       the pharmaceutical industry?

19       **A.**     Yes.

20       **Q.**     The ICH Guideline includes guidelines for impurity  
21       levels?

22       **A.**     Yes.

23       **Q.**     And in particular, the ICH Guidelines includes a  
24       qualification threshold at 0.15 percent for impurities  
25       that are present?

**Pandrapragada - Cross**

1       **A.**    Yes.

2       **Q.**    In the '465 patent, Claims 1 and 10 set an impurity  
3       limit of 0.15 percent for each of Impurities 1 through 3,  
4       5 and 6.

5       **A.**    Yes.

6       **Q.**    And the decision to set the claimed impurity limit at  
7       0.15 for Impurities 1 through 3, 5, and 6 was based off of  
8       the ICH Guideline.

9       **A.**    Yes.

10      **Q.**    You discussed a little bit on your direct examination  
11      HPLC.

12           Do you recall that?

13      **A.**    Yes.

14      **Q.**    You do not necessarily need to know the structural  
15      identity of an impurity for its presence to be detected by  
16      HPLC; is that correct?

17      **A.**    For detection?

18      **Q.**    For detention via HPLC.

19      **A.**    No, you do not need the structure. But, yeah.

20      **Q.**    If HPLC shows the purity of tasimelteon, the total  
21      purity is 99.9 percent, the tasimelteon necessarily has  
22      less than 0.15 of each of Impurities 1 through 3, 5 and 6.

23      **A.**    If the method is sensitive enough to detect all  
24      the impurities that may be present, yeah, it could be.

25      **Q.**    And if you then decide that you want to identify the



**Pandrapragada - Cross**

1 structure of an impurity that you detected, you could run  
2 other tests, correct?

3 **A.** Can you repeat the question again, please?

4 **Q.** Sure.

5 If after detecting an impurity through HPLC if you  
6 wanted to determine the structure of that impurity, you  
7 could run other tests like LCMS or NMR?

8 **A.** Yes.

9 **Q.** And LCMS and NMR are the common tests that someone  
10 would use to identify impurities that have been detected?

11 **A.** Yes, that are used.

12 **Q.** Now let's turn to BMS.

13 Prior to Vanda's work on tasimelteon, BMS had  
14 synthesized tasimelteon.

15 **A.** Yes.

16 **Q.** And you mentioned that in 2004 Vanda entered into a  
17 license agreement with BMS.

18 **A.** Yes, that's correct.

19 **Q.** Could you turn in your binder, please, to JTX-103.

20 **A.** Yes.

21 **Q.** JTX-103 is the license, development, and  
22 commercialization agreement between BMS and Vanda?

23 **A.** From the title, yes. Looks like.

24 **MS. WELLS:** Move to admit JTX- 103 into  
25 evidence.

**Pandrapragada - Cross**

1                   **MS. YOUNG:** No objection.

2                   **THE COURT:** All right. It's admitted.

3                   (JTX- 103 admitted into evidence.)

4                   **BY MS. WELLS:**

5                   **Q.** This license agreement provided Vanda an exclusive  
6 license to BMS's patent covering tasimelteon, correct?

7                   **A.** I cannot comment on that because this is the document  
8 that I never seen before, and I'm not aware of the content  
9 of this document.

10                  **Q.** You are not sure if Vanda has an exclusive license to  
11 BMS's patents?

12                  **A.** It has -- as far as I am aware, Vanda has license.  
13 But the content of the document, this is the first time I  
14 am looking at this document. I'm not aware of this  
15 license agreement so I cannot comment on it.

16                  **Q.** Okay. Are you aware that the license agreement  
17 between BMS and Vanda gave Vanda a license to BMS's  
18 know-how regarding tasimelteon and the manufacture of  
19 tasimelteon?

20                  **A.** Again, I do not have the awareness of any of the  
21 language in this document.

22                  **Q.** Okay. Are you aware that Vanda has received, as part  
23 of the license agreement, a copy of the BMS's documents  
24 data and information regarding tasimelteon and the  
25 manufacture of tasimelteon?

**Pandrapragada - Cross**

1     **A.**     Based on the information that I have seen, there are  
2     documents from BMS, yes.

3     **Q.**     Okay.

4                 **MS. WELLS:** Mr. Brooks, could we please pull up  
5     Page 20, and go to Section 4.1.2.

6     **BY MS. WELLS:**

7     **Q.**     And we see here, Dr. Pandrapragada, it says: 4.1.2.  
8     Copies of documents. BMS shall provide Vanda with one  
9     copy of all documents, data or other information  
10    controlled by BMS to the extent that such documents, data  
11    and information are the subject of the BMS know-how  
12    licenses, and are in BMS's good faith judgment reasonably  
13    necessary for the development, manufacture or  
14    commercialization of the compounds.

15                Did I read that correctly?

16    **A.**     Yes.

17                **MS. WELLS:** And if we could turn, Mr. Brooks,  
18    to Page 7, and look at Section 1.5, BMS know-how.

19    **BY MS. WELLS:**

20    **Q.**     Do you see, Dr. Pandrapragada, it defines BMS  
21    know-how as the BMS compound know-how and the BMS  
22    manufacturing know-how?

23    **A.**     Yes, I see it.

24    **Q.**     And for the compound --

25                **MS. WELLS:** If we could go, Mr. Brooks, to

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Page 8, it's Section 1.1.2.

**BY MS. WELLS:**

**Q.** -- we see there that for compound, it lists a couple different ones, but the first one there, the BMS-214778, that compound corresponds to tasimelteon, correct?

**A.** Yes, that is.

**Q.** And during your work at Vanda, you testified that you reviewed BMS documents that discussed BMS's work on tasimelteon?

**A.** Yes, I have, yes.

**Q.** Part of why you reviewed BMS's documents, was to understand BMS's development history and the process that BMS used to synthesize tasimelteon?

**A.** Yes.

**Q.** If you could turn, please, in your binder to JTX- 117.

**A.** Yes.

**Q.** JTX- 117 is an excerpt from BMS's IND?

**A.** Yes.

**MS. WELLS:** I move to enter JTX- 117 into evidence.

**MS. YOUNG:** No objection.

**THE COURT:** All right. It's admitted.

(PTX-117 is admitted into evidence.)

1 **BY MS. WELLS:**

2 **Q.** BMS's IND included BMS's manufacturing process?

3 **A.** Yes.

4 **MS. WELLS:** And if we could turn, Mr. Brooks,  
5 to JTX- 117, and Page 6 in particular.

6 And if we could pull up the schematic on the  
7 second half of the page there.

8 **BY MS. WELLS:**

9 **Q.** The schematic shows an excerpt from BMS's  
10 manufacturing process?

11 **A.** Yes.

12 **Q.** And you can see some chemical compounds on the  
13 right-hand side, but the top chemical compound that's  
14 labeled BMS-23-7829-01, that's a carboxamide?

15 **A.** Yes.

16 **Q.** And the compound below that that's labeled  
17 BMS-22-0965-02, that's a methanamine?

18 **A.** Yes.

19 **Q.** And the compound below that that's labeled  
20 BMS-21-4778-01, that's tasimelteon?

21 **A.** Yes.

22 **Q.** So this BMS manufacturing document shows that the  
23 carboxamide is contacted reacted with a reducing agent and  
24 an acid to yield methanamine?

25 **A.** Can you repeat the question again?

1 Q. Sure.

2 A. Carboxamide.

3 Q. Sure.

4 The carboxamide is reacted with a reducing agent and  
5 an acid, and that step yields the methanamine?

6 A. The acid is for the Step 2 of the process. First, it  
7 forms -- reacts with the reducing agent to form the amine.  
8 And then the hydrochloric acid is to form the salt of the  
9 amine.

10 Q. Okay. Thank for that clarification. That's a very  
11 important clarification.

12 So the carboxamide in BMS's process is reduced by a  
13 reducing agent and that forms methanamine?

14 A. Yes.

15 Q. That methanamine is then reacted with an acid, and  
16 that forms a methanamine salt?

17 A. Yes.

18 Q. All right. And that methanamine salt in BMS's  
19 process, is then propionylated with a propionylating  
20 reagent to yield tasimelteon?

21 A. Yes.

22 Q. Is that correct?

23 All right. I'd like to turn now to Vanda's NDA.

24 You were involved in reviewing the NDA submission  
25 that Vanda submitted to the FDA; is that correct?

**Pandrapragada - Cross**

1       **A.**     Yes.

2       **Q.**     If you could turn in your binder to DTX- 73.

3       **A.**     I have two binders. Which one?

4       **Q.**     I'm not sure. There should hopefully only be one tab  
5       that says DTX- 73.

6       **A.**     Yes.

7       **Q.**     Are you there?

8             DTX- 73 is the impurity section of Vanda's NDA?

9       **A.**     Yes, that is correct.

10            **MS. WELLS:** Move to introduce DTX- 73 into  
11       evidence.

12            **MS. YOUNG:** No objections.

13            **THE COURT:** It's admitted.

14            **MS. WELLS:** And if we could turn, Mr. Brooks,  
15       to DTX- 73.9.

16            (DTX-73 is admitted into evidence.)

17       **BY MS. WELLS:**

18       **Q.**     And in particular, if we could, look at the first  
19       paragraph under the header 2.1.2.1. It's right in the  
20       smack of the middle of the page. Perfect.

21       **A.**     Okay.

22       **Q.**     So we see here that what Vanda wrote to the FDA in  
23       its NDA says: Tasimelteon was manufactured, first by BMS,  
24       then by Shasun, and most recently by Formosa. The  
25       evolution of the manufacturing process is described in

1 Section 3.2.S.2.6.

2 And the following sentence says: The chronographic  
3 conditions used by these three manufacturers to measure  
4 related substances in tasimelteon drug substance is the  
5 same -- are essentially identical.

6 When it's referring there to related substances, that  
7 means impurities?

8 **A.** Yes.

9 **Q.** And then the next sentence says: Therefore, a direct  
10 comparison of the impurities present in the tasimelteon  
11 drug substance lots and the level of each impurity can be  
12 performed.

13 Did I read that correctly?

14 **A.** Yes, to the best of my knowledge.

15 **Q.** All right.

16 **A.** A comparison could be possible, yes.

17 **Q.** I'm sorry. I missed that.

18 **A.** A comparison is possible, yes.

19 **Q.** A comparison is possible. Okay.

20 **MS. WELLS:** And so if we scroll down,  
21 Mr. Brooks, to the table that's directly below this  
22 paragraph.

23 **BY MS. WELLS:**

24 **Q.** This table is providing the relative retention times  
25 for known impurities present in the tasimelteon from the



**Pandrapragada - Cross**

1 three different manufacturers, correct? BMS, Shasun and  
2 Formosa?

3 **A.** Yes.

4 **Q.** We see there's a column on the left-hand side that  
5 says "the impurity," and then there are three columns  
6 listing each manufacturer individually?

7 **A.** Yes.

8 **Q.** If we could go down. The table continues on to the  
9 top of the next page.

10 So I'm interested in Impurity 5, which is the  
11 third-from-the-bottom row of the table.

12 Do you see that row, Dr. Pandrapragada?

13 **A.** Yes.

14 **Q.** Impurity 5, that's the Impurity 5 in the '465 patent?

15 **A.** Impurity 5? Yes.

16 **Q.** And in parentheses, it says "Impurity P5"?

17 Do you see that?

18 **A.** Yes, I see that.

19 **Q.** Impurity P5 is the nomenclature that BMS used?

20 **A.** Yes, they have used.

21 **Q.** So we see here that in its NDA, Vanda was telling the  
22 FDA that Impurity 5, which BMS referred to as Impurity P5,  
23 was present in the BMS lot, as well as Formosa; is that  
24 correct?

25 **A.** I don't think the comparison of these impurities was

**Pandrapragada - Cross**

1 directly correlated with these. Not are the same as what  
2 BMS had. We only compared this because no other retention  
3 times were close enough, so -- but I don't believe. It's  
4 not necessarily Impurity 5 is exactly same as Impurity P5.

5 **Q.** So when Vanda wrote in its NDA Impurity 5 (Impurity  
6 P5), and then said it was in the BMS lot and Formosa lot,  
7 you don't think Vanda was telling the FDA that Impurity 5  
8 was actually in the BMS lot?

9 **A.** I don't believe we said Impurity P5 is the same as  
10 Impurity 5. But we just correlated the data from BMS  
11 that -- just because the relative retention times were  
12 close enough. And also, Impurity P5 was present in BMS  
13 lots. But I don't believe there is a structure that was  
14 identified BMS -- by BMS for Impurity P5.

15 **Q.** Okay. So your testimony here today is that when  
16 Vanda said that BMS impurity at retention time 1.50 was  
17 Impurity 5, they were only saying that because it was  
18 similar to the retention time of Impurity 5 that was  
19 measured in a different lot?

20 **A.** I think the relative retention times were very close  
21 enough, so that the only reason why we were giving the  
22 benefit of the doubt, it could be or it could not be. But  
23 there is no definitive information that is present in BMS  
24 documents that -- to show there are impurities in  
25 Impurity 5.

**Pandrapragada - Cross**

1     **Q.** But the relative retention time of 1.5 -- there  
2     actually was an impurity that's shown in Shasun and  
3     Formosa at retention time 1.5, right, and that's listed as  
4     Impurity 3?

5     **A.** Yes. But the chromatographic conditions were  
6     relatively different compared to the BMS lots. So the  
7     Impurity 3 that is presented 1.50 as Formosa is actually  
8     the Impurity 3 that we identified later.

9     **Q.** So you think it was a mistake to list Impurity 5  
10    (Impurity P5) on this chart and show that it was in both  
11    BMS and Formosa's lots?

12    **A.** I don't believe it is a mistake. But it was just  
13    benefit of the doubt. Like when we just had that  
14    information, that that's close enough if you compare with  
15    the BMS lots.

16    **Q.** That 1.48 was close enough to 1.5?

17    **A.** That's our thinking when we prepared this document.  
18    But it was just the thought -- that's the only close  
19    enough data we could see in BMS lots if we wanted to  
20    compare the impurities.

21    **Q.** Okay. Let's see what else Vanda said in its NDA  
22    about this Impurity P5.

23           **MS. WELLS:** Mr. Brooks, if we could please turn  
24    to DTX- 73.8. And look at the second-to-last paragraph.

25

**Pandrapragada - Redirect**

1 **BY MS. WELLS:**

2 **Q.** All right. Here, Vanda told the FDA: Impurity P1  
3 was identified in BMS from LCMS and NMR data.

4 And then in the sentence they said -- or Vanda said:  
5 Impurities P2, P3, P4 -- and importantly for our purposes  
6 here today -- P5 were identified at BMS from LCMS and  
7 LCNMR data.

8 Did I read that correctly?

9 **A.** Yes. Based off of the information that I read, yes.  
10 That's the P2, P3, P4, and P5, P1 were present in the IND  
11 documents.

12 **Q.** In the BMS IND documents?

13 **A.** Yes.

14 **Q.** Okay. And the LCMS and LCNMR, those are the tools  
15 that you testified earlier are the common ways that  
16 someone would identify an impurity?

17 **A.** Yes.

18 **Q.** Dr. Pandrapragada, you have never worked for BMS?

19 **A.** No.

20 **Q.** And prior to July of 2010, you performed no work  
21 related to tasimelteon or the synthesis of tasimelteon?

22 **A.** No.

23 **MS. WELLS:** No further questions, Your Honor.

24 **THE COURT:** Thank you.

25 Redirect?

**Pandrapragada - Redirect**

REDIRECT EXAMINATION

**BY MS. YOUNG:**

**Q.** Mr. Pandrapragada, do you recall being asked if you needed to know the structure of an impurity in order to detect it on an HPLC?

**A.** Yes.

**Q.** How do you know whether or not your HPLC can detect the impurity if you don't know the structure?

**A.** If we don't know the structure, there are some -- all depends on the type of detection that you use in the HPLC.

Yes, during the initial development, you need to know what type of compound it is, whether what type of detection system that you can use for HPLC.

So if it has a UV absorption, then you use UV detector. And for certain molecules, they don't have cytochrome that can be observed in the UV. So those compounds cannot be detected in HPLC.

But, yes, you need to know literally about a compound structure whether or not you can use the HPLC to detect the impurities, but it enables us to decide what type of detector can be used along with HPLC to protect those impurities.

**Q.** And do you recall being asked whether Impurity 5 is the same as P5?

**A.** Yes.

**Pandrapragada - Redirect**

1     **Q.**    Do you recall whether BMS proposed a structure for  
2     P5?

3     **A.**    No, they did not propose a structure for P5.

4                 **MS. YOUNG:**   And if you could -- Mr. Weir, if  
5     can you pull up JTX- 117.

6                 Mr. Weir can you pull up JTX- 117.   It should  
7     be in the binder that you were just looking at.

8                 **THE WITNESS:**   Yes.

9     **BY MS. YOUNG:**

10    **Q.**    Do you recall Ms. Wells asking you about this  
11    document?

12    **A.**    Yes.

13    **Q.**    And if you could turn to Page 54, please.

14                 **MS. YOUNG:**   And if, Mr. Weir, you can blow up  
15    that structure on the bottom, including the text below it.

16                 **THE WITNESS:**   Yes.

17    **BY MS. YOUNG:**

18    **Q.**    Do you see there where it says:   Isomeric impurities  
19    at RRT 1.35, 1.39 and 1.50?

20    **A.**    Yes, I can see it.

21    **Q.**    What is being shown there?

22    **A.**    That is a proposed structure tentatively assigned  
23    based on the NMS in this data.

24    **Q.**    How does that structure compare to the structure for  
25    Impurity 5?

**DeCicco Video Clip**

1       **A.**     It is different than what is shown here.

2               **MS. YOUNG:**   I have no further questions.

3               **THE COURT:**   All right.   Thank you.

4               You can step down.   Thank you.   All right.

5               **MR. STONE:**   Your Honor, it's -- we have about  
6       15, ten minutes worth of video in total that we intend to  
7       play.   Should we do it now?

8               We are going to bring up binders with the clips  
9       in it.   Thank you, Your Honor.

10              My colleague, Michael Milea, will introduce who  
11     the witnesses are in terms of their name before they are  
12     each played.

13              **MR. MILEA:**   Good afternoon, Your Honor.  
14     Michael Milea on behalf of Vanda Pharmaceuticals.

15              The first clip will be from David DeCicco  
16     30(b)(6) witness for Teva.

17              (Video clip played.)

18       **"Q.**   How long have you worked at Teva?

19       **"A.**   About three years.

20       **"Q.**   What's your current title?

21       **"A.**   Director of regulatory affairs.

22       **"Q.**   Can you describe to me your roles and  
23     responsibilities in your current position?

24       **"A.**   I'm responsible for review and approval of  
25     submissions that are going to the FDA from various R&D

***Shah - Video Clip***

1 facilities as well as commercial facilities.

2 **MR. KLEIN:** Marking Exhibit 40.

3 "Q. Do you recognize this document, Mr. DeCicco?

4 "A. Yes.

5 "Q. What do you recognize it to be?

6 "A. A copy of our draft outsert for tasimelteon capsules.

7 "Q. Is a draft outsert another way of saying prescribing  
8 information or drug label?

9 "A. Yes.

10 "Q. Who's the intended audience of this document?

11 "A. The patients.

12 "Q. Not the physicians?

13 "A. It would be them as well, too.

14 "Q. Does Teva have an understanding of how prescribers  
15 treat patients using tasimelteon?

16 "A. Just what's listed in the labeling.

17 "Q. Does Teva expect prescribers of its generic  
18 tasimelteon product to follow the language in its proposed  
19 label for generic tasimelteon?

20 "A. That would be my understanding to follow what's in  
21 the labeling.

22 (Video clip ends.)

23 **MR. MILEA:** Your Honor JTX- 29 which was shown  
24 in that video, I believe that's already into evidence.

25 The next clip will be from Dr. Vatsal Vittahl



**Shah - Video Clip**

1 Shah also a 30(b)(6) witness.

2 (Video clip played.)

3 "Q. Would you please state your full name for the record.

4 "A. It's Vatsal Vitthal Shah.

5 "Q. Who do you currently work for?

6 "A. So just to clarify, are you asking about the company?

7 "Q. Yes, the company?

8 "A. Teva Pharmaceuticals.

9 "Q. Can you please describe your current  
10 responsibilities?

11 "A. So my current role is a director of portfolio  
12 management and I'm responsible for selection of products  
13 into the Teva pipeline.

14 "Q. Once Teva receives FDA approval of its ANDA, how --  
15 what will Teva do with the capsules manufactured at the  
16 Goa site?

17 "A. So again, I don't know whether Teva would launch  
18 right after it will get FDA approval. But generally  
19 speaking, once the clearance is received to launch the  
20 product from our attorneys, it will be manufactured and  
21 then imported into the US from the Goa site.

22 "Q. Has Teva determined what or how it will import the  
23 capsules into the United States?

24 "A. So the capsules -- the finished capsules would be  
25 bought by Teva Pharmaceuticals USA, Inc. and then they'll

1 be imported or would be sold to that entity into the US.

2 "Q. Who will distribute the capsules in the United  
3 States?

4 "A. I think it's Teva Pharmaceuticals USA, Inc.

5 "Q. What Teva entities are or will be involved in  
6 manufacturing the tasimelteon product?

7 "A. I guess it is the same facility in India, the Goa  
8 facility in India.

9 (Video clips ends.)

10 **MR. MILEA:** The next clip is Mr. Bhupesh Singh  
11 a 30(b) (6) witness of Apotex.

12 (Video clip played.)

13 "Q. Would you please state your name for the record.

14 "A. My full name is Bisht Bhupesh Perni Singh.

15 "Q. Can you please describe your current  
16 responsibilities.

17 "A. So my current responsibilities are managing  
18 submissions for the US strategizing submissions that come  
19 from our various affiliate sites for the US market,  
20 managing in licensed and co-development -- co-development  
21 partners. That is basically -- and -- and managing FDA  
22 and communication around it.

23 "Q. I'm going to mark Apotex Exhibit 27. What is this  
24 document?

25 "A. This is the product label for the Apotex generic

1 tasimelteon submitted to the agency for review.

2 "Q. Why is Apotex proposing a label for its tasimelteon  
3 product?

4 "A. As -- as -- as a requirement to file the product, we  
5 need to also supply a summary to FDA, a -- a labeling that  
6 covers the product, and which should match as the brand  
7 labeling is -- not the brand, the reference listed drug  
8 labeling is. And that's why this label has been  
9 submitted, because this is what is required by the FDA  
10 laws to submit an application.

11 "Q. What's the purpose of this label?

12 "A. This -- the purpose of the label is to guide the  
13 physicians and to know more about the product and the  
14 molecule.

15 "Q. Does Apotex have an understanding of what the dosage  
16 regime will be for its generic tasimelteon product?

17 "A. Like I said, the dosage regime is as per the labeling  
18 that is approved for the brand and that is what we have to  
19 follow. And that's what is there on our label.

20 "Q. Does Apotex expect prescribers prescribing its  
21 generic tasimelteon product to follow its proposed label  
22 for tasimelteon?

23 "A. Like I said, we -- we don't interact with  
24 prescribers, but it is up to their best judgment how to  
25 prescribe the product.

1       **"Q.** Do you expect that prescribers will follow the  
2       information in Apotex's label when prescribing the  
3       tasimelteon product?

4       **"A.** Like I said, this is based on each physician's  
5       understanding and prescribing behavior. I would expect  
6       them to follow what is supplied with the product.

7       **"Q.** And the label is supplied with the product?

8       **"A.** That's correct.

9       (Video clip ends.)

10       **MR. MILEA:** Your Honor, JTX- 31, which was  
11       shown in that clip is an older version of the Apotex label  
12       that was marked during prior testimony, and so we'd like  
13       to offer JTX- 31 into evidence.

14       **MR. COBLENTZ:** JTX- 29, no objection.

15       **MR. MILEA:** Older version of Teva labeled  
16       discussed during prior testimony we would like to offer  
17       that into evidence as well.

18       **MR. ROZENDAAL:** No objection.

19       **THE COURT:** All right. It's admitted.

20       (JTX-29 admitted into evidence.)

21       **MR. MILEA:** The last clip is Dr. Martin Ehlert  
22       also of Apotex.

23       (Video clip is played.)

24       **"Q.** Would you please state your full name for the record.

25       **"A.** Martin Kurt Ehlert.

1           **"Q.** Can you describe your current responsibilities.

2           **"A.** Yes. So my title is vice president Global API, R&D.

3           And so the areas at the business for which I have

4           responsibility are essentially anything to do with the

5           provision of active pharmaceutical ingredients to the

6           Apotex group of companies for development of drug

7           products. So as I had mentioned briefly in the summary of

8           my work experience, it includes any technical matters

9           associated with APIs procured from third parties. And I

10          should say it also will include, when required, technical

11          matters associated with excipients used in drug products

12          which are the nonmedicinal ingredient as well I have

13          corporate level responsibility for research and

14          development on active pharmaceutical ingredients. And

15          then I act as a connecting person in that sense with our

16          drug product development teams. I think that summarizes

17          my responsibilities.

18          **"Q.** What is your educational background?

19          **"A.** I have a PhD in chemistry and I have an undergraduate

20          degree in what's termed applied chemistry, a mix of

21          chemistry and chemical engineering.

22          **"Q.** Earlier, we discussed after Apotex's ANDA is

23          approved, Apotex would be importing capsules of

24          tasimelteon. Do you remember that?

25          **"A.** I do remember the discussion. Yes.

1           **"Q.** Is Apotex Incorporated the entity that will be  
2           importing the capsules from Canada into the United States?

3           **"A.** Apotex, Inc. is actually the exporter from Canada  
4           into the US inbound will be Apotex Corp.

5           **"Q.** Is Apotex Corp. distributing the product once it  
6           enters the United States?

7           **"A.** Yes.

8           (Video clip ends.)

9                   **MR. MILEA:** That's it for our video clips, and  
10           I should have also mentioned that Dr. Ehlert is a 30(b)(6)  
11           witness for Apotex.

12                   **THE COURT:** So you all could have stipulated to  
13           those facts? I had to hear 15 minutes of deposition  
14           testimony tell me which Teva, which Apotex organizations  
15           did what.

16                   I mean, was there any discussion at all about  
17           that? And you all insisted you needed 15 hours each. I  
18           said 13. I'm trying to figure this out.

19                   **MR. STONE:** Your Honor, with respect to the  
20           half of the clips that were about intent beyond the label,  
21           that is something that is, essentially, in every one of  
22           these cases of whether the defendant is going to say their  
23           knowledge is limited to the label or there is knowledge  
24           beyond that. With respect the importation clips, I take  
25           the Court's point for sure. The reason it arises is that

1 as Your Honor, I'm sure, knows from prior cases --

2 **THE COURT:** That may not be true. Don't assume  
3 anything.

4 **MR. STONE:** Imagine that there's a  
5 manufacturing patent, a method of making this, Section  
6 271(g) says if you sell in the US, this having made it  
7 outside the US, while the manufacturing patent is in  
8 force, you are an infringer of the manufacturing patent.  
9 It's designed to prevent people from manufacturing  
10 offshore to avoid a US manufacturing patent.

11 The impurities patent in this case is sort of a  
12 weird hybrid, as Mr. Rozendaal said, it is a claim to the  
13 product, but it has to be made in a certain way, and there  
14 is a question in the law that's open right now as to  
15 whether that provision and how it is applied to product by  
16 process claims.

17 And so that we are not accused at some point of  
18 having failed to prove that the product is not altered  
19 upon importation, we put on, you know, ten minutes, at  
20 most, of testimony that this one makes it in India, that  
21 one makes it Canada, but, yes, they are bringing it into  
22 the US, and yes, it is the same. It is not the most  
23 important point in the world. I was afraid of being told  
24 on appeal that we had footfaulted. So that was the reason  
25 for putting it into evidence. I take the Court's point.

1           **THE COURT:** It is a question. I don't  
2 understand why not talk about it, instead of there being  
3 discussions is what I'm trying to figure out. I get the  
4 impression nobody ever sat down and said, I think we can  
5 stipulate to these things.

6           **MR. STONE:** I think we have not done an  
7 adequate job on both sides of trying to figure out some of  
8 the smaller areas in which we agree to save time. I think  
9 we have a very good sense of the bigger issues on which we  
10 disagree. I take the Court's point, and I apologize.

11           **THE COURT:** So on the label that actually, you  
12 said that there's -- they don't have to rely on the label.  
13 I thought we were in an ANDA case, and you do have to rely  
14 on the label.

15           **MR. STONE:** You are absolutely correct, Your  
16 Honor. We think that they do, and that they are deemed to  
17 intend the contents of the label.

18           There have been cases in the past in which  
19 generics have attempted to argue, I don't have any idea  
20 what anyone does with the label. I am a tabula rasa. So  
21 we wanted to establish that each of these defendants  
22 admits that they understand that doctors will, in fact,  
23 follow the label. I think that's deemed law anyway but --

24           **THE COURT:** That's what I wanted to get at  
25 because certainly from my perspective, having prosecuted,



1 brought civil cases against, you know, folks on behalf of  
2 the United States when they deviated from the label, I  
3 don't know how you get away with saying you are not going  
4 to rely on the label. But there are patent cases that do  
5 allow for that, you are saying?

6 **MR. STONE:** I am not sure they do allow it for.  
7 I think the argument has been made. I think the current  
8 state of the law is they don't allow for it.

9 For example, there was a significant case in  
10 the Federal Circuit in the last year involving GSK.

11 **THE COURT:** Judge Stark's case?

12 **MR. STONE:** I believe it is Judge Stark's case,  
13 and then in one of the cases I was looking at earlier --

14 **THE COURT:** That case, I thought, was post -- I  
15 thought they were on the market.

16 **MR. GROOMBRIDGE:** They were.

17 **THE COURT:** That's a different story.

18 **MR. STONE:** We read the law the way Your Honor  
19 does, which is that in an ANDA case, if the label  
20 instructs, recommends, suggests or encourages the acts of  
21 infringement, they induce infringement. But there is  
22 enough reason to wonder whether that will be the argument  
23 and the state of the law that we felt it was worth proving  
24 that they have no other knowledge beyond what is in the  
25 label.

1 I think you are correct about the law, Your  
2 Honor.

3 **THE COURT:** You are taking that position  
4 anyway, aren't you? In this case, you are going to argue  
5 it against them, right?

6 **MR. ROZENDAAL:** Yes, Your Honor. I think we  
7 intend to say that we intend that the label will be  
8 followed according to what it instructs.

9 **THE COURT:** Right. You are going to use that  
10 against them.

11 **MR. ROZENDAAL:** Not more than that.

12 I will say for the record, I don't think that  
13 271(g) is an issue in this case. I think we have a  
14 product claim and not a process claim, but, certainly, our  
15 colleagues from Vanda are extremely thorough. If they  
16 have identified an open issue that I am not aware of, I  
17 will take them at their word.

18 **THE COURT:** All right. Well, I mean, I think  
19 you are down to 12 hours each on your total. You are  
20 expressing frustration. There's been no meaningful meet  
21 and confers, obviously, to try to streamline this case.

22 You know, you all could have talked about some  
23 of these things, and I think it's incumbent upon lawyers  
24 to do that.

25 I don't mean to sound preachy because I have

1 really good lawyers here. I mean, you know, the Court's  
2 time is a precious resource.

3 The only whip I've got is to reduce your time,  
4 right.

5 **MR. STONE:** I understand, Your Honor. I'm not  
6 looking to stick my head in the lion's mouth.

7 The only thing I would say is that we are  
8 exactly where we thought we were going to be at the end of  
9 the day. We have one witness left who we are going to  
10 greatly streamline, and there is a disproportion --  
11 disproportion impact is a loaded phrase. I don't mean it  
12 that way.

13 We bear the burden significantly of lowering  
14 the hour when our case is essentially complete because we  
15 have put on -- we could have shortened a witness had we  
16 known they were stipulating to it. I understand --

17 **THE COURT:** The fault is on both sides in terms  
18 of stipulation. There's been no discussion.

19 **MR. STONE:** By lowering both sides' time when  
20 we have been doing direct and --

21 **THE COURT:** They have invalidity. I thought  
22 the time would affect them. I'm asking.

23 **MR. STONE:** I don't think it does, Your Honor.

24 **MR. ROZENDAAL:** I think it certainly will, Your  
25 Honor. I think we have a lot more material to get through

1 on invalidity than they have to go through today for  
2 infringement.

3 **MR. STONE:** We're going to find out, Your  
4 Honor. Thank you.

5 **THE COURT:** What I'll do is I will leave it at  
6 13. As many complements I have thrown to both sides, next  
7 time you're at pretrial conference and you tell me you  
8 think it's 15 hours, you are never getting it, you know.

9 The other thing I am mandating that counsel  
10 confer tonight, and I need both Delaware lawyers, and two,  
11 you know, you have a lot of lawyers here, a lot in court.  
12 I don't know who the lead lawyer is, but I'm going to make  
13 it -- I'm going to go by age, maybe.

14 Mr. Groombridge, Mr. Rozendaal -- and your  
15 name, sir?

16 **MR. COBLENTZ:** Mr. Coblantz.

17 **THE COURT:** Mr. Coblantz, Mr. Hoeschen and  
18 Ms. Jacobs, you must meet this evening, and it has to be  
19 productive.

20 You have to meet in person. You have to meet  
21 in a room, and it's got to be -- I'm going to ask you how  
22 long you met because a lot of this stuff should go away.

23 It's going to make it easier post trial. It's  
24 going to benefit your clients because you will pare down  
25 the issues that are really important, and that should have

1       been done coming in here.

2               I am afraid to pull the trigger on absolute  
3       reduction to 12 hours. It really should be 11. I don't  
4       know where it should be.

5               My colleagues try these cases in 20-to-22  
6       hours, they inform me. I've been doing it and getting  
7       through with 20 hours, and I've yet to have a lawyer say  
8       they couldn't try the case at the end of the case. They  
9       got it through.

10              So that's where we are. Is there anything else  
11      that needs to be resolved this evening?

12              **MR. GROOMBRIDGE:** I don't think there's  
13      anything else from us, Your Honor.

14              **MR. ROZENDAAL:** I don't believe we have issues  
15      to resolve, Your Honor.

16              I will flag a possible scheduling issue for  
17      later in the week. So we have a witness, Dr. Greenblatt.

18              **MR. COBLENTZ:** Dr. Greenblatt, I think we made  
19      you aware at the pretrial conference, that he is  
20      unavailable until Thursday morning. And so I don't know  
21      how that will work with the scheduling, whether we are  
22      working it out. That's one of the things we will talk  
23      about tonight a little more, about how to streamline this  
24      to make Wednesday be a fuller day, so we're not just  
25      waiting on Dr. Greenblatt to testify.

1                   **THE COURT:** Okay. You think he might be the  
2 last witness on Thursday?

3                   **MR. STONE:** No, Your Honor. He is an  
4 invalidity witness for them. We have two witnesses who  
5 are directly responding to his testimony.

6                   We are prepared to call everybody else in our  
7 case before he testifies, but I can't -- so if they want  
8 to finish their invalidity case, other than Greenblatt, we  
9 will start our rebuttal case at that point, hold their  
10 invalidity case open. I can't call the two witnesses who  
11 are responding to Greenblatt until Greenblatt happens.

12                   If he can't testify until Thursday morning,  
13 they will have to go Thursday. But we will get everything  
14 else done on our plate on Wednesday; even though, they  
15 haven't finished their case. Essentially, we will let  
16 them call him in our case.

17                   **THE COURT:** Okay.

18                   **MR. COBLENTZ:** What we don't know is that will  
19 mean that there's a little time at the end of Wednesday  
20 that's unfilled. We don't know that yet. It's a matter  
21 of how much the parties streamline the case. So we'll  
22 work through that.

23                   **THE COURT:** Okay. All right. See you in the  
24 morning.

25                   **MR. ROZENDAAL:** Your Honor, what time tomorrow?

1                   **THE COURT:** You all need to be here at  
2                   8:30 because I have a case tomorrow, discovery, where one  
3                   side said they met and conferred; the other side said they  
4                   didn't. I have to address that. And it's a patent case  
5                   surprise, surprise.

6                   That's at 8:30 in my jury room. As soon as  
7                   that's done, I am coming out here. Might be five minutes.  
8                   Might be half hour. You need to be ready to go at 8:30.  
9                   Thank you.

10                  (The proceedings concluded at 5:26 p.m.)  
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CERTIFICATE OF COURT REPORTER

I hereby certify that the foregoing is a true and accurate transcript from my stenographic notes in the proceeding.

/s/ Bonnie R. Archer  
Bonnie R. Archer, RPR  
Official Court Reporter  
U. S. District Court



BY MR. GROOMBRIDGE: [43] 97/23 99/15 102/24 104/24 105/8 106/18 108/24 111/1 111/6 112/1 115/2 118/2 120/17 121/3 121/9 123/15 125/7 126/2 128/3 128/19 132/23 134/1 134/14 136/19 137/21 138/15 139/15 140/5 140/24 145/9 147/6 148/10 149/2 149/13 152/5 152/18 154/20 156/2 156/25 158/2 159/19 192/19 194/11 BY MR. KLEIN: [31] 198/10 198/20 199/9 201/24 202/15 202/24 203/22 205/15 206/21 208/1 208/6 209/3 209/24 211/1 211/10 212/3 218/24 220/4 220/20 221/13 222/24 223/4 224/6 224/21 229/20 231/9 231/22 233/5 235/7 235/12 253/8 BY MR. MILLIKEN: [10] 160/10 164/19 166/21 170/11 172/9 176/8 180/24 190/2 190/17 192/2 BY MR. PICKARD: [7] 237/2 237/22 243/2 243/10 244/24 250/22 252/7 BY MS. WELLS: [10] 287/13 290/4 291/6 291/19 292/2 292/25 293/8 295/17 296/23 299/25 BY MS. YOUNG: [28] 254/14 255/2 255/20 256/19 257/24 258/12 260/19 262/9 266/1 266/6 268/25 269/6 270/15 271/18 272/3 276/17 279/14 279/23 280/11 281/6 281/23 282/17 284/22 285/9 286/20 301/2 302/9 302/17 DR. 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